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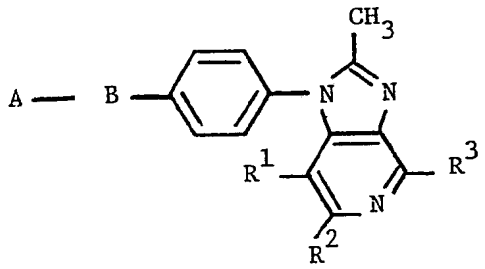
(54) Title: IMIDAZOPYRIDINE PAF ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I), wherein A is a C_1-C_8 alkyl, perfluoroalkyl, cycloalkyl, aryl, substituted aryl, heterocyclic or substituted heterocyclic group; B is defined to include a variety of linking groups including straight and branched-chain alkylene and alkenylene groups as well as groups containing an ether, thio-ether, amine or amide group and various substituted and cyclic variations thereof; and R^1, R^2 and R^3 are each H or CH_3; are PAF antagonists of value in the treatment of allergic and inflammatory conditions in humans.

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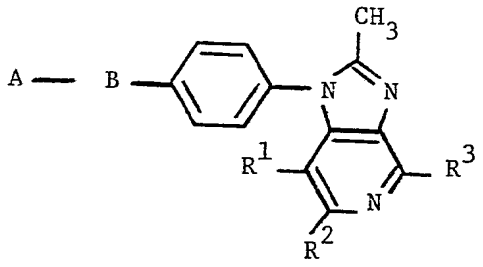
IMIDAZOPYRIDINE PAF ANTAGONISTS

This invention relates to imidazopyridines specifically to certain 4-substituted-1-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzene derivatives. The compounds are potent and selective antagonists of platelet activating factor having clinical utility in the treatment of allergic and inflammatory conditions in humans and animals.

Platelet activating factor (PAF, 1-O-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine) is an ether phopholipid whose structure was first elucidated in 1979. It is produced by, released from and interacts with many pro-inflammatory cells, platelets and the kidney. In addition to potent platelet aggregating activity, PAF exhibits a wide spectrum of biological activities elicited either directly or via the release of other powerful mediators such as thromboxane A_2 or the leukotrienes, which make PAF inhibitors of potential value in the treatment of a variety of conditions including allergic, inflammatory and hypersecretory conditions such as asthma, arthritis, rhinitis, bronchitis and urticaria, the treatment of circulatory shock, gastric ulceration, psoriasis and cardiovascular conditions, including angina, thrombosis and stroke.

In our European patent application no 0258033 we disclose a series of 2-substituted 1,4-dihydropyridine derivatives as PAF antagonists. In our later European patent application no 0310386 we disclose a further series of dihydropyridine PAF antagonist wherein the 2-position substituent includes in particular a 2-methyl-imidazo[4,5-c]pyrid-1-yl-phenyl group. The present invention provides further PAF antagonists having the formula:



....(I)

and pharmaceutically acceptable salts thereof,

wherein A is a C_1-C_8 alkyl, perfluoro(C_1-C_8)alkyl, C_3-C_8 cycloalkyl, aryl or heterocyclic group, wherein said aryl or heterocyclic group may be unsubstituted or substituted with from one to three substituents each independently chosen from C_1-C_4 alkyl, halo, oxo, CO_2R^4, $CONR^5R^6$, OH, C_1-C_4 alkoxy, NH_2, NO_2, CN and $(CH_3)_3SiCH_2$;

B is a C_1-C_5 alkylene or C_2-C_5 alkenylene chain which may optionally be substituted by one or more C_1-C_4 alkyl, C_1-C_4 alkoxy, perfluoro(C_1-C_4)alkyl, C_3-C_7 cycloalkyl, phenyl, oxo, OH, CN, $CONR^5R^6$ or CO_2R^4 groups and wherein up to two carbon atoms in said chain can independently be replaced by O, $S(O)_m$, -N= or NR^7, and wherein said chain or part of said chain, may form, or may form part of, a 5-7 membered saturated or mono-unsaturated ring which may contain a nitrogen atom or NR^7 group, a nitrogen and oxygen atom, or one or two oxygen atoms, said ring being optionally substituted with any of the foregoing chain substituents, and, in the case where the group A is an aryl or heterocyclic group, the ring may optionally be fused to said aryl or heterocyclic group;

each of R^1, R^2 and R^3 is independently H or CH_3;

R^4 is H, C_1-C_4 alkyl or aryl(C_1-C_4)alkyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or R^5 is H and R^6 is C_3-C_8 cycloalkyl or aryl, or the two groups R^5 and R^6 together with the nitrogen atom to which they are attached, form a piperidino, 4-ketopiperidino, morpholino or piperazinyl group;

R^7 is H, C_1-C_4 alkyl, CO_2(C_1-C_4)alkyl, aryl(C_1-C_4)alkyl or heteroaryl(C_1-C_4)alkyl;

and m is 0, 1 or 2;

with the proviso that A-B is not $C_2H_5OCOCH_2CO$- or $CH_3COCH_2CO_2CH_2$-.

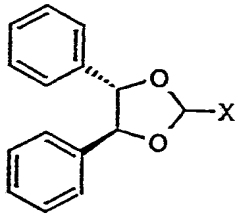
In the above definitions, the term aryl includes phenyl, naphthyl, tetrahydronaphthyl and indanyl, each of said groups being optionally substituted as defined in A above; alkyl groups having 3 or more carbon atoms may be straight or branched-chain; and halo means fluoro, chloro, bromo or iodo. In the definition of A, the term heterocyclic group means a 5 or 6 membered ring containing up to four nitrogen atoms, or one or two nitrogen atoms together with a further oxygen or sulphur atom, or up to two oxygen atoms or a sulphur atom, as heteroatom, and said ring may be saturated or unsaturated and substituted with one or more subsitutuents as defined in A above, and may optionally be fused to a phenyl or further 5 or 6 membered heterocyclic ring. Examples of particular heterocyclic groups include pyridyl, quinolyl, benzimidazolyl, benzthiazolyl, benzdioxolanyl, benzothienyl, triazolyl, imidazolyl, indazolyl, indolinyl, piperidyl and morpholinyl.

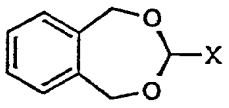
The term heteroaryl used in relation to R^7 means a 5 or 6 membered aromatic heterocyclic group including, for example, pyridyl, thienyl and imidazolyl.

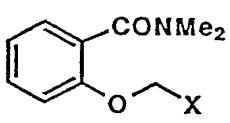
As defined above a variety of linking groups B, are possible and as well as simple straight-chain or branched alkylene and alkenylene groups, the invention includes groups containing an ether, thioether, amine or amide group and various cyclic variations thereof:

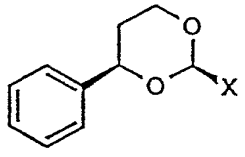
a) Thus, in one particular aspect of the invention the linking group, B, is an ether group having an oxygen atom and up to four carbon atoms in the chain linking the group A to the phenyl ring. The linking group may optionally have a further oxygen atom in the chain and said chain may optionally be substituted by hydroxy, oxo (to give an ester group), C_1-C_4 alkoxy, C_1-C_4 alkyl or phenyl. In this embodiment the linking group may also form part of a 5 to 7 membered cyclic ether group containing one or two oxygen atoms in the ring which may optionally be substituted by C_1-C_4 alkyl hydroxy, oxo, or C_1-C_4 alkoxy and which may optionally be fused to a phenyl or tetrahydronaphthalene ring. Thus the ring may be for example, a tetrahydropyranyl, dioxolanyl, dioxanyl or dioxepanyl ring.

In this aspect the group, A, is preferably a phenyl group which may optionally be substituted as defined in A above. Thus particular and preferred examples of this type include compounds of the following formulae-:

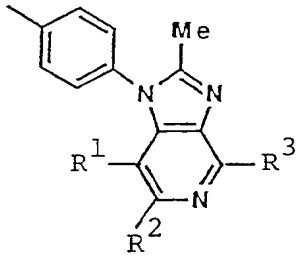








wherein X is:



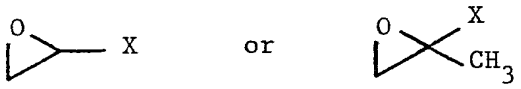
R^1, R^2 and R^3 being preferably H.

Compounds of this type may be prepared by a variety of methods as will be known to those skilled in the art. In one process the ethers are prepared by reaction of the corresponding hydroxyalkyl derivative of formula:

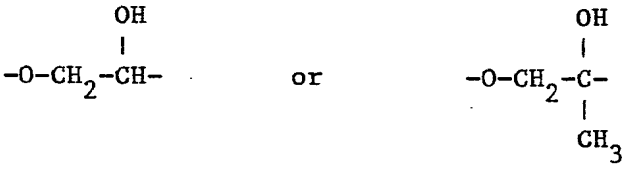
$$HO - D - X \qquad \ldots (II)$$

wherein X is as previously defined and D is C_1-C_4 alkylene group which may optionally be substituted as defined in B above; by reacting with an appropriate phenol or heteroaryl derivative of formula Ar-OH wherein Ar is an aryl or heteroaryl group which may optionally be substituted as defined for A above. The reaction is performed in an inert organic solvent e.g. tetrahydrofuran, in the presence of triphenylphosphine and diethylazodicarboxylate (Mitsunobu reaction). Certain transformation reactions are possible on the products, thus for example when the phenol is substituted by CO_2R^4, wherein R^4 is C_1-C_4 alkyl, hydrolysis will give the corresponding carboxylic acid (wherein R^4 is H). This in turn may be reacted with a variety of amines of formula R^5R^6NH to give the corresponding carboxamide derivatives where the substituent is of formula $CONR^5R^6$ and R^5 and R^6 are as previously defined.

In an alternative process, an oxirane of formula:

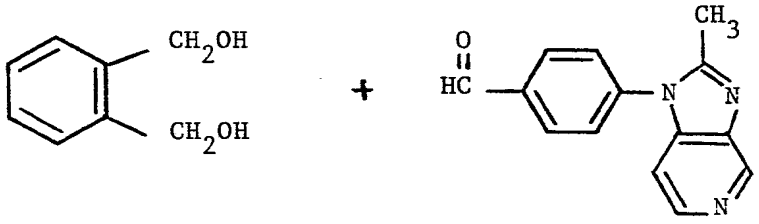


wherein X is as previously defined, may be reacted with a phenolic anion e.g. by heating in dimethylformamide, to give the corresponding compounds of formula(I) wherein the linking group B is



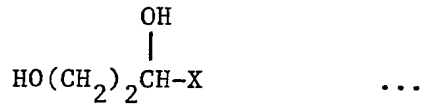
respectively.

Cyclic diethers are readily prepared by reaction of a diol with the appropriate aldehyde or ketone. Thus for example reaction of



yields the corresponding 2,4-benzodioxepine derivative. This reaction may also be performed by using the trimethylsilyl derivative of the diol, following the procedure of T. Tsunoda, M. Suzuki and R. Noyori, Tetrahedron Letters, 1980, 21, 1357.

Other variants are possible, thus for example reaction of a compound of the formula:



... (IV)

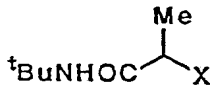
with butyl lithium and chlorotrimethylsilane, followed by reaction with an aldehyde, gives a 2-aryl-dioxane derivative.

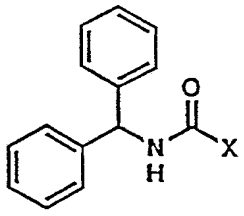
Finally ester-linked derivatives may be prepared by reaction of the carboxylic acid of formula HO_2C-D^1-X with an alkanol of formula $A-D^1-OH$ or by reaction of an alkanol of formula $HO-D^1-X$ with an acid of formula $A-D^1-CO_2H$ wherein A, and X are as previously defined and D^1 is as previously defined for D or it may be a direct bond.

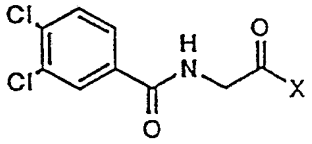
Appropriate reagents and conditions for all of the above reactions are given in standard text books and by reference to the experimental examples given hereafter.

b) In a further aspect of the invention, the linking group B contains an amide group together with up to three further carbon atoms in the chain linking A to the phenyl ring. The nitrogen atom may optionally be substituted by C_1-C_4 alkyl and the chain may optionally be substituted by C_1-C_4 alkyl or phenyl, or include a further oxo substituent. In this embodiment the group A may be phenyl, optionally substituted as defined in A above or it may be naphthyl, indanyl, or a heterocyclic group, for example a pyridyl, quinolyl, indazolyl, benzimidazolyl or benzthiazolyl group.

Thus particular and preferred examples of this type include:







Compounds of this type are generally prepared by reaction of an amine of formula $A-D^1-NHR^{19}$ with an acid of formula HO_2C-D^1-X, wherein R^{19} is H or C_1-C_4 alkyl and A, D^1 and X are as previously defined. The reaction may conveniently be achieved via the acid chloride which may be prepared by reaction of the acid with, for example, oxalyl chloride in accordance with normal practice. Alternatively an amine of formula

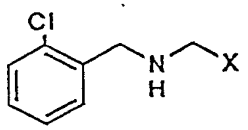
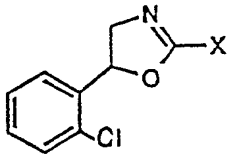
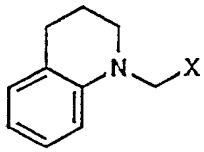
$$R^{19}NH-D^1-X \quad \ldots (VI)$$

may be reacted with a carboxylic acid of formula $A-D^1-CO_2H$ in an analgous manner.

c) In another aspect of the invention, the linking group contains NR^7 or -N=, together with up to four carbon atoms in the chain, which may optionally be substituted by oxo or $CO_2(C_1-C_4)$alkyl. The amino substituent R^7 is preferably H, C_1-C_4 alkyl, $CO_2(C_1-C_4)$alkyl or aryl(C_1-C_4)alkyl. The linking group in this case may optionally be cyclised to form a pyrrolidinyl group or piperidino group, which may optionally be fused to a benzene ring, or it may be an oxazoline ring.

In this aspect the group A is preferably phenyl, optionally substituted as previously defined.

Thus particular and preferred examples include:

Compounds of this type may be prepared by reductive alkylation of an arylamine or aryl(C_1-C_4)alkylamine with an aldehyde of the formula

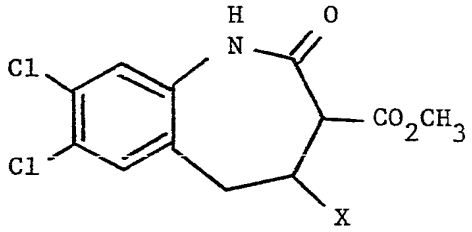
$$HCO\text{-}D^1\text{-}X \qquad \ldots (VII)$$

wherein X and D^1 are as previously defined.

The reaction is readily achieved via reduction of the Schiff's base using, for example, sodium borohydride or sodium cyanoborohydride. A number of further transformation reactions are possible on the product, as previously described thus, for example, an aryl-nitro group may be reduced to the corresponding amino compound, for example using stannous chloride and, in the case of the 2-aminoanilinomethyl derivative, this may be cyclised by reaction with triethylorthoformate to the corresponding benzimidazolylmethyl derivative. Further reactions include, for example, reaction of the amine products with n-butyl lithium followed by reaction with a C_1-C_4 alkylchloroformate to give the N-alkoxycarbonyl derivatives, or alkylation to give the products where R^7 is C_1-C_4 alkyl, aryl(C_1-C_4 alkyl) or heteroaryl(C_1-C_4)-alkyl.

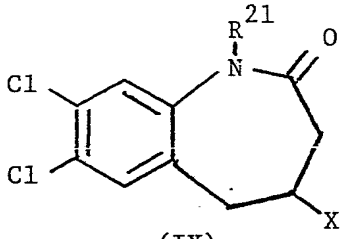
d) In a further aspect of the invention, the linking group B is a 7 membered saturated or mono-unsaturated ring containing $-NR^7-$ wherein R^7 is as previously defined. The ring may optionally be

substituted as previously defined under B; preferred substituents include oxo and CO_2R^4, particularly when R^4 is methyl. R^7 is preferably H, C_1-C_4 alkyl, aryl(C_1-C_4)alkyl or heteroaryl(C_1-C_4)-alkyl. In this embodiment A is preferably phenyl or substituted phenyl and said phenyl ring is benzofused to the 7-membered ring B. Thus particular and preferred compounds of this type include-:



(VIII)

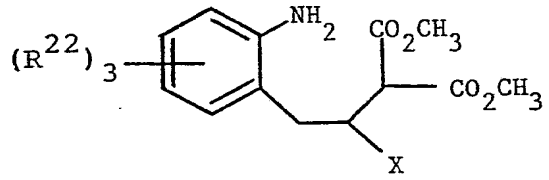
and



(IX)

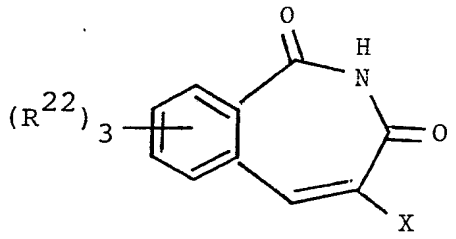
wherein R^{21} is H, methyl, 4-chlorobenzyl or 2-pyridylmethyl and X is as previously defined.

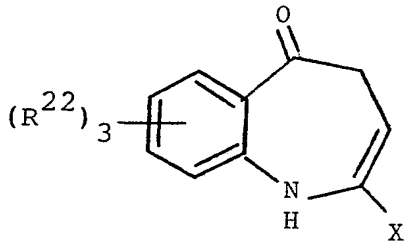
The above compounds are prepared by cyclisation of a compound of the formula:



wherein each R^{22} is independently H or an aryl group substituent as defined in A above, to give the 3-methoxycarbonyl-tetrahydro-benzazepin-2-one (VIII). Subsequent treatment by heating in pyridine with lithium iodide gives the tetrahydrobenzazepin-2-one (IX) (R^{21}=H), which may subsequently be alkylated on nitrogen by reaction with a strong base, e.g. sodium hydride, followed by reaction with the appropriate alkyl or substituted-alkyl halide to give the 1-substituted-tetrahydrobenzazepin-2-ones.

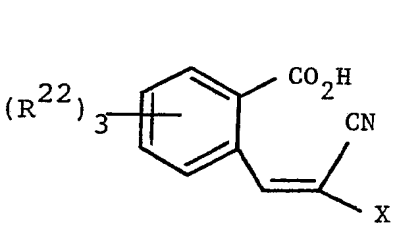
Further particular and preferred compounds of this type include-:

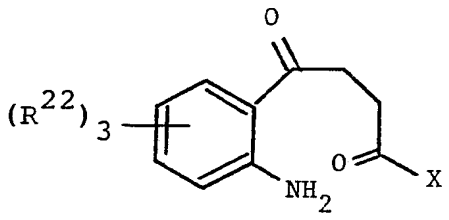




wherein X is as previously defined and R^{22} is preferably H.

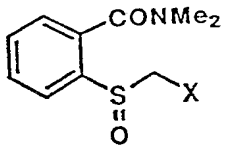
These compounds are prepared by ring closure of the corresponding open chain compound of formula:

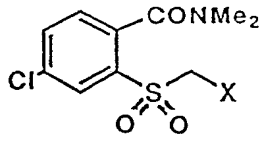




respectively by heating under acidic conditions.

e) In a further aspect of the invention the linking group B contains a $S(O)_m$ group together with up to four carbon atoms where m is 0-2 . Thus the sulphur atom may be present as a thioether, sulphone or sulphoxide group. The chain may optionally be substituted by C_1-C_4 alkyl or hydroxy. The group A is preferably phenyl optionally substituted as previously defined in A above. Particular and preferred examples of this type include:



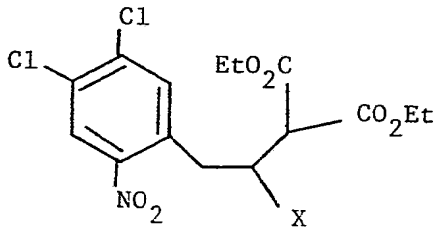


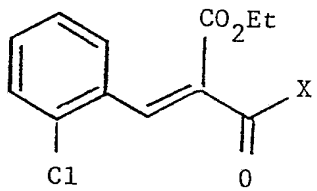
Compounds of this type may be prepared by reaction of an aryl or aralkyl thiol of formula A-D^1-SH with an alcohol of formula HO-D^1-X in the presence of triphenylphosphine and diethylazodicarboxylate to give compounds where the linking group B is -D^1-S-D^1-, wherein each D^1 is as previously defined with the proviso that the number of atoms in the chain linking A to the phenyl ring does not exceed 5.

As before conventional transformation reactions can be performed on the products, for example to give the aryl-carboxamide derivatives via hydrolysis of the corresponding esters and reaction of the resulting carboxylic acid with an amine.

The sulphones and sulphoxide derivatives (m = 1 or 2) can be prepared from the thioethers by conventional oxidation, for example using meta-chloroperbenzoic acid.

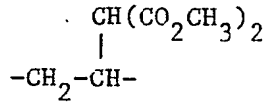
f) Finally, in a further aspect of the invention, the linking group B is a C_1-C_4 alkylene or alkenylene group which may optionally be substituted by one or more OH, oxo, CO_2R^4 or perfluoroalkyl groups. The group A is preferably phenyl optionally substituted as defined in A above or is heptafluoropropyl. Thus examples of preferred compounds include:



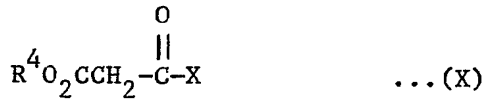


Compounds of this type may be prepared by a number of different methods. In one procedure the aldehyde of formula (VII) may be reacted with dimethylmalonate followed by reaction with the anion derived from 4,5-dichloro-2-nitrotoluene, to provide the compound

of formula (I) wherein the linking group B is a dimethyl ethylmalonate group of formula:

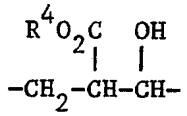


Alternatively reaction of an aryl aldehyde with a ketoester of formula (X):

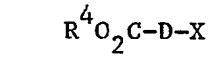


...(X)

wherein R^4 is C_1-C_4 alkyl and X is as previously defined, yields the 3-aryl-2-alkoxycarbonylprop-2-ene-1-one derivative. Reduction gives the 3-aryl-2-alkoxycarbonyl-1-hydroxypropyl derivative where the linking group is-:



Further possibilities include the reaction of aldehyde (VII) with a benzyl triphenylphosphonium bromide or chloride to give 1-aryl ethene derivatives. Finally reaction of an ester of formula:



wherein R^4 is C_1-C_4 alkyl and D and X are as previously defined, by reaction with, for example, a perfluoroalkyl magnesium iodide, gives the corresponding perfluoroalkyl-carbonyl derivative. The ketone may be further reacted, for example with a further Grignard addition to give further disubstituted-methanol derivatives.

All of the reactions described in a) to f) above are entirely conventional and alternative methods and procedures to all of the compounds within the scope of claim 1 will be evident to those skilled in the art. Appropriate reagents and conditions for their performance may be readily established by reference to standard

text books and to the examples provided hereafter.

The compounds may be purified using conventional methods such as recrystallisation or column chromatography as appropriate, and compounds having acidic or basic centres may be isolated as the free acid or base or in salt form. Compounds having asymmetric centres may be isolated as the racemic mixtures or resolved to give the individual enantiomers. The invention includes all enantiomers whether resolved or not.

The pharmaceutically acceptable acid addition salts of the compounds of the formula (I) which form such salts are those formed from acids which form non-toxic acid addition salts, for example the hydrochloride, hydrobromide, sulphate or bisulphate, phosphate or acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methane-sulphonate, benzenesulphonate and p-toluenesulphonate salts.

The activity of the compounds of the invention is shown by their ability to inhibit the platelet aggregating activity of PAF in vitro. Testing is performed as follows:

Blood samples are taken from either rabbit or man into 0.1 vol disodium ethylenediamine tetraacetic acid buffer and the samples centrifuged for 15 minutes to obtain platelet rich plasma. The plasma is further centrifuged to give a platelet pellet which is washed with a buffer solution (4 mM KH_2PO_4, 6mM Na_2HPO_4, 100 mM NaCl, 0.1% glucose and 0.1% bovine serum albumin, pH 7.25) and finally resuspended in buffer solution to a concentration of 2×10^8 platelets/ml. A sample (0.5 ml) is pre-incubated with stirring for two minutes at 37°C in a Paton aggregometer, either with vehicle alone, or with vehicle containing the particular

compound under test. PAF is added at a sufficient concentration to give a maximum aggregating response in the absence of test compound. (10^{-8} to 10^{-9} molar), and the platelet aggregation is measured by following the increase in light transmission of the solution. The experiment is repeated in the presence of test compound at a range of concentrations and the concentration of compound required to reduce the response to 50% of its maximum value is recorded as the IC_{50} value.

The activity of the compounds of formula (I) is also demonstrated in vivo by their ability to protect mice from the lethal effect of an injection of PAF. A mixture of PAF (50 μg/kg) and DL-propranolol (5 mg/kg) in 0.9% w/v sodium chloride is injected (0.2 ml) via a tail vein into mice. The compounds under test are either injected into the tail vein immediately prior to the PAF/propranolol injection or administered orally by gavage two hours earlier. The compounds are tested at several doses in groups of 5 mice and the dose which reduces mortality to 50% is recorded as the PD_{50} value.

For therapeutic use the compounds of the formula (I) will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For administration to man in the curative or prophylactic treatment of allergic bronchial conditions and arthritis, oral dosages of the compounds will generally be in the range of from 2-1000 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 1 to 500 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration would typically be within the range 1 to 10 mg per single dose as required. For the treatment of allergic and bronchial hyper-reactive conditions, inhalation via a nebuliser or aerosol may be the preferred route of drug administration. Dose levels by this route would be within the range 0.1 to 50 mg per single dose as required. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the

particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of the formula (I), without proviso, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention also includes a compound of the formula (I), without proviso, or a pharmaceutically acceptable salt thereof, for use in medicine, in particular in the treatment of allergic, inflammatory and hypersecretory conditions in a human being.

The preparation of the compounds of the invention is further illustrated by the following Examples.

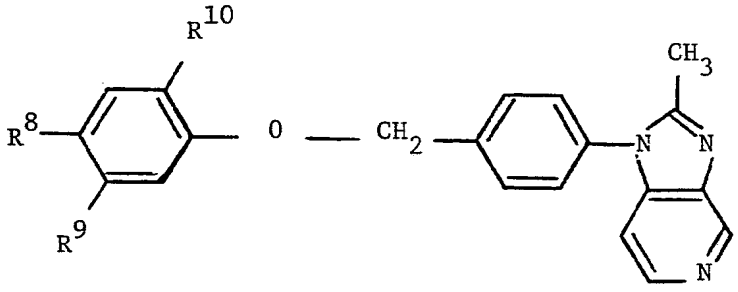
EXAMPLE 1

Methyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]benzoate

A mixture of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (2.39 g, 10 mmol), methyl salicylate (1.67 g, 11 mmol), triphenylphosphine (2.88 g, 11 mmol) and dry tetrahydrofuran (50 ml) was stirred at room temperature under nitrogen. Diethylazodicarboxylate (2.09 g, 12 mmol) was added dropwise over five minutes. The resulting solution was stirred at room temperature for 1 hour and the solvent then removed under reduced pressure. The residue was purified by chromatography on silica eluting with a mixture of dichloromethane and methanol (97:3). The product containing fractions were combined and evaporated to dryness. The residue was crystallised from diethyl ether to yield the title product (3.42 g, 92%), m.p. 126-128°C.
Found: C,70.92; H,5.11; N,11.17. $C_{22}H_{19}N_3O_3$ requires C,70.78; H,5.09; N,11.26%.

EXAMPLES 2-8

The following compounds were made following the procedure of Example 1 using the appropriate phenol as starting material.



Example No	R^8	R^9	R^{10}	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
2	H	CH_3	CO_2CH_3	179-181	71.04 (71.32	5.66 5.43	10.96 10.85)
3	CH_3	H	CO_2CH_3	123-125	71.23 (71.32	5.55 5.43	10.98 10.85)
4	Cl	H	CO_2CH_3	136-138	64.46 (64.79	4.47 4.42	10.22 10.31)
5	H	Cl	CO_2CH_3	154-156	64.64 (64.79	4.37 4.42	10.12 10.31

Example No	R^8	R^9	R^{10}	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
6	H	H	Cl	123-125	68.85	4.63	12.00
					(68.67	4.58	12.02)
7	Cl	H	H	171-174	67.38	4.53	11.68
					(67.51	4.69	11.81)
8	F	H	F	108-110	68.38	4.25	11.93
					(68.38	4.27	11.97)

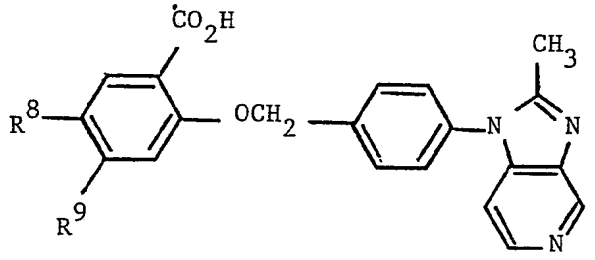
EXAMPLE 9

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]benzoic acid

Methyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]-benzoate (3.73 g, 10 mmol) was dissolved in ethanol (100 ml), 2N sodium hydroxide (20 ml) added and the solution stirred at room temperature for 2 hours. The solvent volume was reduced to 30 ml under reduced pressure and the residue poured into water (100 ml). The aqueous phase was washed with dichloromethane (2 x 50 ml) and acidified with glacial acetic acid. The acid mixture was then extracted with dichloromethane (3 x 75 ml) and the combined acid extracts dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure to yield a white solid. Trituration with diethyl ether gave the pure title product (2.03 g 57%). m.p. 217-219°C. Found: C,68.48; H,4.89; N,11.41. $C_{21}H_{17}N_3O_3$ 0.5 H_2O requires C,68.65; H,4.73; N,11.21%.

EXAMPLE 10-13

The following compounds were prepared in a similar manner from the appropriate benzoate of Examples 2-5.



Example No	R^8	R^9	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
10	H	CH_3	227-229	68.90 (69.11 (0.5 mole H_2O)	5.18 5.24	10.82 10.99)
11	CH_3	H	212-214	70.14 (69.93 (0.5 mole H_2O)	5.31 5.17	11.05 11.13)
12	H	Cl	219-221	61.43 (61.24 (hydrate)	4.02 4.37	9.94 10.21)
13	Cl	H	219-221	63.74 (64.04	4.17 4.07	10.71 10.67)

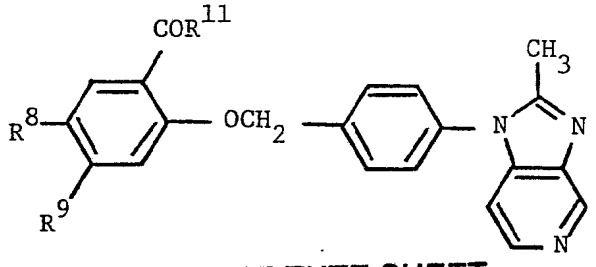
EXAMPLE 14

N,N-Dimethyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]-benzamide

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]benzoic acid (359 mg, 1 mmol) was stirred in dichloromethane (15 ml) and 3 drops of N,N-dimethylformamide were added. Oxalyl chloride (254 mg, 2 mmol) was added dropwise over 1 minute. The resulting solution was stirred at room temperature for 30 minutes then evaporated to dryness. The residue was redissolved in dry dichloromethane (5 ml) and added dropwise to an ice-cold solution of dimethylamine (1 ml) in ethanol (9 ml) over a five minute period. The mixture was stirred at 0°C for 30 minutes and the solvent then evaporated to dryness. The residue was stirred in ethyl acetate (100 ml), the solution washed with water (2 x 50 ml), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was further purified by chromatography on silica eluting with a mixture of dichloromethane and methanol (96:4) and the product containing fraction were combined and evaporated to dryness. The crude product was crystallised from diethyl ether (258 mg, 67%) m.p. 148-150°C. Found: C,71.12; H,5.78; N,14.29. $C_{23}H_{22}N_4O_2$ requires C,71.50; H,5.70; N,14.51%.

EXAMPLES 15-21

The following compounds were prepared from the corresponding benzoic acid following the above procedure.

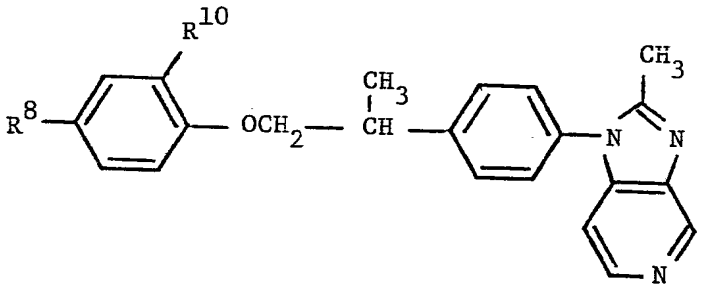


Example No	R^8	R^9	R^{11}	m.p. °C	Analyisis % (Theoretical in brackets)		
					C	H	N
15	H	H	NH_2	226-228	68.15	4.97	14.94
					(68.11	5.22	15.14)
					(0.67 mole H_2O)		
16	H	H	$NHCH_3$	207-209	70.34	5.39	14.81
					(70.12	5.44	14.87)
					(0.25 mole H_2O)		
17	CH_3	H	$NHCH_3$	193-195	71.11	5.79	14.55
					(71.50	5.70	14.51)
18	Cl	H	$N(CH_3)_2$	184-186	65.29	5.10	13.26
					(65.64	4.99	13.32)

Example No	R^8	R^9	R^{11}	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
19	H	CH_3	$NHCH_3$	225-227	69.30	5.56	14.17
					(69.09	5.88	14.02)
					(0.75 mole H_2O)		
20	Cl	H	$NHCH_3$	229-231	64.33	4.83	13.21
					(64.23	4.74	13.63)
					(0.25 mole H_2O)		
21	H	Cl	$NHCH_3$	204-206	64.54	4.76	13.40
					(69.94	4.67	13.78)
21(a)	H	Cl	$N(CH_3)_2$	194-196	64.19	4.98	12.85
					(64.26	5.16	13.03)
					(0.5 mole H_2O)		

EXAMPLES 22-29

The following compounds were prepared using the procedure of Example 1, starting with 2-methyl-2-[4-(2-methylimidazo[4,5-c]-pyrid-1-yl) phenyl]propan-1-ol and reacting with the appropriate phenol, followed by conversion to the corresponding acid or amide following the procedures of Examples 9 and 14 as appropriate.



Example No	R^{10}	R^{8}	m.p. °C	Analysis %. (Theoretical in brackets) C	H	N
22	F	F	94-96	69.54 (69.66	5.03 5.01	10.93 11.08)
23	H	Cl	146-148	70.10 (69.93	5.52 5.30	10.74 11.13)
24	Cl	H	136-138	70.06 (69.93	5.47 5.30	10.87 11.13)
25	CO_2CH_3	H	125-127	71.87 (71.82	5.87 5.74	10.55 10.41)
26	COOH	H	133-136	69.51 (69.70 (0.5 mole H_2O)	5.74 5.56	10.36 10.61)

Example No	R^{10}	R^8	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
27	$-CONH_2$	H	218-220	67.23	5.55	13.61
				(66.82	6.05	13.56)
				(1.5 mole H_2O)		
28	$-CONHCH_3$	H	200-202	69.73	6.04	13.54
				(69.65	6.17	13.54)
				(0.75 mole H_2O)		
29	$-CON(CH_3)_2$	H	148-150	71.71	6.39	13.23
				(71.68	6.33	13.88)
				(0.25 mole H_2O)		

EXAMPLE 30

1-(4-[2-Chlorophenoxyethylphenyl])-2-methylimidazo[4,5-c]pyridine

2-Chlorophenol (0.87 mmol, 112 mg), 1-[4-(2-hydroxyethyl-phenyl)]-2-methylimidazo[4,5-c]pyridine (0.87 mmol, 220 mg) and triphenylphosphine (0.87 mmol, 228 mg) were dissolved in dry tetrahydrofuran (10 ml). Diethylazodicarboxylate (0.87 mmol, 151 mg) was added dropwise and the solution stirred for 24 hours, then evaporated to dryness. The residue was purified by column chromatography on silica eluting with dichloromethane and methanol (97:3), and the product-containing fractions evaporated to dryness to give an oil (0.23 g, 73%) which crystallised on standing. M.p. 111-113°C. Found: C,68.78; H,4.96; N,11.47. $C_{21}H_{18}ClN_3O$ 0.25 H_2O requires C,68.48; H,5.06; N,11.41%.

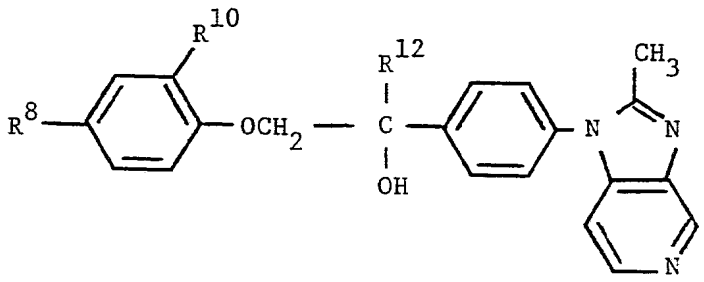
EXAMPLE 31

1-(2-Chlorophenoxy)-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]propan-2-ol

A mixture of 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-methyloxirane (133 mg, 0.5 mmol), 2-chlorophenol (129 mg, 1 mmol) and potassium carbonate (138 mg, 1 mmol) was stirred in N,N-dimethylformamide (5 ml) at 90°C under nitrogen for 10 hours. The cooled mixture was poured into brine (50 ml) then extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was further purified by column chromatography on silica eluting with dichloromethane/methanol (97:3). The product-containing fractions were evaporated to dryness and the crude product crystallised from diethyl ether. (119 mg, 61%). m.p. 225-227°C. Found: C,66.95; H,5.24; N,10.36. $C_{22}H_{20}ClN_3O_2$ requires C,67.09; H,5.08; N,10.67%.

EXAMPLES 32-36

The following compounds were prepared as described above using the appropriate oxirane and phenol as starting materials:



Example No	R^{12}	R^{10}	R^{8}	m.p. °C	Analyisis % (Theoretical in brackets) C	H	N
32	H	F	F	156-158	66.34 (66.14	4.45 4.46	10.92 11.02)
33	H	Cl	H	174-176	66.51 (66.40	4.72 4.74	10.99 11.07)
34	H	H	Cl	188-191	66.30 (66.40	4.76 4.74	10.98 11.07)
35	CH_3	F	F	201-203	66.74 (66.84	4.97 4.81	10.34 10.63)
36	CH_3	H	Cl	166-168	66.90 (67.09	5.09 5.08	10.59 10.67)

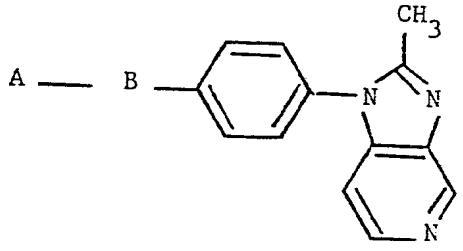
EXAMPLE 37

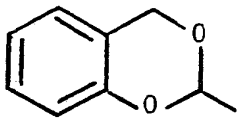
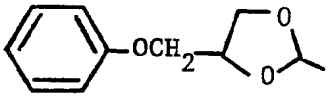
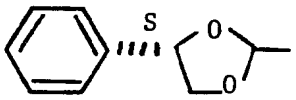
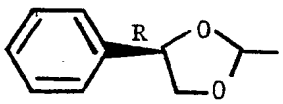
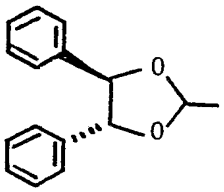
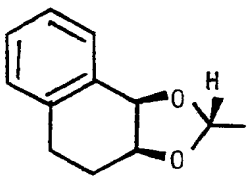
2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,3-benzo[e]-dioxepane

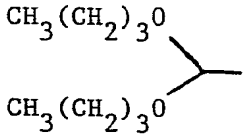
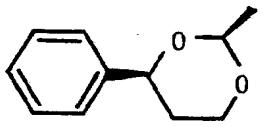
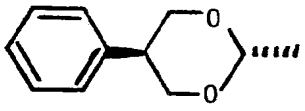
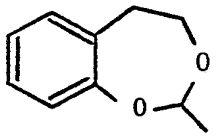
p-Toluenesulphonic acid hydrate (0.23 g, 1.2 mmol) was added in small portions to a boiling solution of 4-(2-methyimidazo[4,5-c]pyrid-1-yl)-benzaldehyde (0.23 g, 1 mmol) and 1,2-bis-hydroxy-methyl-benzene (0.16 g, 1.2 mmol) in dichloromethane (6 ml). This mixture was refluxed through a soxhlet thimble containing 4 Angstrom molecular sieves for 2 hours, then partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulphate and the solvent evaporated to yield a foam which was crystallised from ethyl acetate/diethyl ether (0.3 g, 82%). m.p. 142-144°C. Found: C,73.29; H,5.38; N,11.32. $C_{22}H_{19}N_3O_2$ requires C,73.93; H,5.36; N,11.76%.

EXAMPLES 38 - 47

The Examples in the following Tables were prepared following the above procedure reacting 4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzaldehyde with the appropriate diol or with butanol.



Example No	A-B-	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
38		foam	72.33	5.36	11.25
			(72.51	4.98	11.53)
			(0.25 mole $CH_3CO_2C_2H_5$)		
39		glass	70.40	5.66	10.26
			(70.39	5.55	10.63)
			(0.25 mole $CH_3CO_2C_2H_5$)		
40		61	73.22	5.62	11.18
			(72.82	5.58	11.07)
			(0.5 mole $CH_3CO_2C_2H_5$)		
41		51-53	73.68	5.59	11.33
			(73.93	5.36	11.76)
42		88-89	76.60	5.47	9.34
			(76.40	5.53	9.22)
			(0.25 mole $CH_3CO_2C_2H_5$)		
43		foam	73.02	5.72	10.36
			(73.05	5.89	9.86)
			(0.5 mole $CH_3CO_2C_2H_5$)		

Example No	A-B-	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
44		oil	70.92	8.02	10.79
			(70.61	7.96	10.95)
			0.25 mole $CH_3CO_2C_2H_5$)		
45		154-6	74.02	5.70	10.99
			(74.37	5.70	11.31)
46		148-50	74.37	5.80	11.40
			(74.37	5.70	11.31)
47		157-9	72.26	5.39	11.41
			(72.11	5.50	11.47)
			(0.5 mole H_2O)		

EXAMPLE 48

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-methyl-4-phenyl-1,3-dioxolane

Neat 1,2-bis(trimethylsilyloxy)-1-phenylethane (0.17 g, 0.6 mmol) was added to a cold (-78°C), stirred solution of trimethylsilyl trifluoromethanesulphonate (0.1 ml) in dichloromethane (1 ml). After 5 minutes, a solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)acetophenone (0.13 g, 0.5 mmol) in dichloromethane (1 ml) was added. The resultant solution was warmed to 20°C during 2 hours, then stirred for 72 hours before partitioning between dichloromethane and saturated sodium bicarbonate solution. The organic layer was washed with brine, dried over magnesium sulphate and evaporated to a yellow oil. Silica gel chromatography using 10% methanol in ethyl acetate as eluant afforded a colourless foam (0.1 g, 48%). The product was a 1:3 mixture of cis/trans isomers. m.p. less than 40°C. Found: C,72.56; H,5.85; N,10.53. $C_{23}H_{21}N_3O_2.\frac{1}{2}H_2O$ requires C,72.61; H,5.83; N,11.04%.

EXAMPLE 49

2-(2-Chlorophenyl)-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,3-dioxane

Butyllithium (1.6M in hexane; 0.91 ml, 1.46 mmol) was added in drops to a stirred suspension of 1-[4-(1,3-dihydroxypropyl)-phenyl]-2-methylimidazo[4,5-c]pyridine (0.2 g, 0.7 mmol) in anhydrous tetrahydrofuran. The mixture was heated to reflux for 30 minutes, then cooled and treated with chlorotrimethylsilane

(0.22 ml, 1.7 mmol). After stirring for 16 hours, the solvent was evaporated and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried over magnesium sulphate and concentrated to an oil. To a solution of this oil in anhydrous dichloromethane (5 ml) at 0°C were added sequentially a solution of trimethylsilyl trifluoromethane-sulphonate (0.18 ml, 0.92 mmol) in dichloromethane (1 ml) followed by 2-chlorobenzaldehyde (0.1 g, 0.7 mmol). The mixture was stirred at ambient temperature for 24 hours, and then partitioned between dichloromethane and saturated, aqueous sodium bicarbonate. The organic layer was dried over magnesium sulphate and evaporated to an oil. Silica-gel chromatography eluting with 10% methanol in ethyl acetate and trituration with diethyl ether afforded a white solid (0.15 g, 52%), m.p. 161-164°C. Found: C,67.81; H,5.02; N,10.14. $C_{23}H_{20}ClN_3O_2$ requires C,68.06; H,4.97; N,10.35%.

EXAMPLE 50

4-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-(3,4,5-trimethoxyphenyl)-1,3-dioxane

The procedure of Example 49 was followed but replacing 2-chlorobenzaldehyde with 3,4,5-trimethoxybenzaldehye in the second stage of the process to yield the title product as a white solid in 28% yield. M.p. 135°C. Found: C,66.95; H,5.97; N,8.82. $C_{26}H_{27}N_3O_5 \cdot 0.25\ H_2O$ requires C,67.01; H,5.95; N,9.02%.

EXAMPLE 51

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-4-phenyl-1,3-dioxolane

1,2-Bistrimethylsilyloxy-1-phenylethane (from Preparation 6) (0.34 g, 1.2 mmol) was added to a cold (-70°C), stirred solution of trimethylsilyl trifluoromethane-sulphonate (0.23 ml, 1.2 mmol) in dry dichloromethane (2 ml). After 5 minutes, a solution of 4-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzaldehyde (0.24 g, 1 mmol) in 2 ml of dichloromethane was added. The mixture was allowed to warm to 22-24°C then stirred at this temperature for 22 hours. The reaction mixture was partitioned between saturated aqueous sodium bicarbonate and dichloromethane, the organic layer was dried ($MgSO_4$) and evaporated to a residue which was purified by silica-gel chromatography (5% methanol in ethyl acetate as eluant) to afford the title compound as a foam (0.031g, 8%). Found: C,71.37; H,5.39; N,10.83. $C_{22}H_{19}N_3O_2 \cdot 0.75\ H_2O$ requires C,71.24; H,5.57; N,11.27%.

EXAMPLE 52

2-Chlorobenzyl 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoate

Oxalyl chloride (0.7 ml, 8 mmol) and dimethylformamide (1 drop) were added to a stirred suspension of 4-(2-methylimidazo-[4,5-c]pyrid-1-yl)benzoic acid (0.51 g, 2 mmol) in dichloromethane (10 ml) at 0°C under nitrogen. After 1 hour, the solvent was evaporated and the residue dissolved in dichloromethane (10 ml) to which was added 2-chlorobenzyl alcohol (0.86 g, 6 mmol) and 4-dimethylamino-pyridine (2-3 crystals). After 16 hours, the mixture was diluted with dichloromethane and washed with aqueous sodium carbonate. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Flash chromatography, eluting with 15% methanol in ethyl acetate left a residue which solidified on trituration with diethyl ether (0.255g, 33%). M.p. 147-149°C. Found: C,66.86; H,4.32; N,11.15. $C_{21}H_{16}Cl_2N_3O_2$ requires C,66.76; H,4.27; N,11.12%.

EXAMPLE 53

[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyloxy]diphenylmethane hydrochloride

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (1 mmol, 253 mg), and benzhydrol (1 mmol, 184 mg) were dissolved in dichloromethane (5 ml). Trifluoroacetic acid (0.5 ml) was added dropwise and the mixture stirred for 15 minutes. The solution was poured into 2N sodium hydroxide and the aqueous phase extracted with dichloromethane (3 x 40 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was further purified by column chromatography on silica

gel eluting with dichloromethane/methanol (95:5). The product containing fractions were evaporated to dryness, dissolved in ether and treated with ethanolic hydrogen chloride. The resulting solid was recrystallised from ethyl acetate/methanol, (62 mg, 14%). M.p.235-237°C. Found: C,72.73; H,5.58; N,9.25. $C_{27}H_{23}N_3O.HCl.$ 0.25 H_2O requires C,72.65; H,5.49; N,9.42%

EXAMPLE 54

[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyloxy](2-chlorophenyl)-methane hydrochloride

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (1 mmol, 253 mg) was dissolved in dimethylformamide (10 ml) and sodium hydride (60% in oil, 1.15 mmol, 46 mg) was added and the mixture stirred at room temperature for 1 hour. Freshly distilled chlorobenzyl chloride (1.1 mmol, 177 mg) was added and the mixture stirred for 4 hours at room temperature. The reaction was quenched with 1N hydrochloric acid (1 ml) then basified with 5% sodium carbonate solution and the aqueous phase extracted with dichloromethane (3 x 50 ml). The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica eluting with dichloromethane/methanol (97:3) and the product containing fractions evaporated to dryness. The oil was redissolved in diethyl ether and treated with ethereal hydrogen chloride. The solid precipitate was recrystallised from ethyl acetate/methanol to give the title product, (67 mg, 17%). M.p. 218-220°C. Found: C,62.44; H,4.75; N,10.34. $C_{21}H_{18}ClN_3O.HCl.$ 0.25 H_2O requires C,62.31; H,4.86; 10.38%

EXAMPLE 55

5-(2-Chlorophenyl)-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-delta^2-oxazoline

N-[2-(2-Chlorophenyl)-2-hydroxyethyl]-4-(2-methylimidazo[4,5-c]-pyrid-1-yl) benzamide (0.5 mmol, 200 mg) and triphenylphosphine (0.6 mmol, 157 mg) were dissolved in tetrahydrofuran (5 ml) at room temperature. Diethylazodicarboxylate (0.6 mmol, 104 mg) was added dropwise and the mixture stirred for 12 hours then poured into ether 150 ml) and extracted with 0.5 N hydrochloric acid (2 x 25 ml). The combined aqueous extracts where basified with 2N sodium hydroxide then re-extracted with dichloromethane (3 x 50 ml), dried over $NaSO_4$, filtered and evaporated to dryness. The residue was partially purified by column chromatography eluting with ethyl acetate/diethylamine (97:3), the product-containing fractions were evaporated and the residue further purified by preparative thin-layer chromatography in dichloromethane/methanol (95:5) to give the title product (25 mg, 13%), m.p. 127-130°C. Found: C,67.68; H,4.67; N,13.79. $C_{22}H_{17}ClN_4O$ requires C,67.95; H,4.38; N,14.41%.

EXAMPLE 56

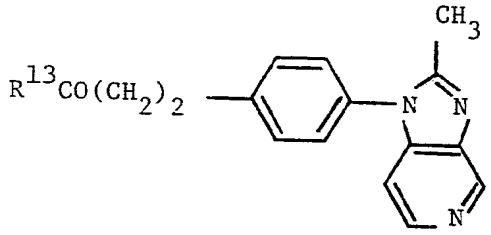
N,N-Diethyl-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-propionamide

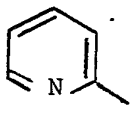
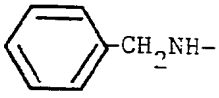
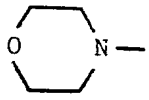
a) Methyl 3-[4-(2-methylimidazo]4,5-c]pyrid-1-yl)phenyl]-propanoate (3.56 mmol, 1.05 g) was dissolved in ethanol (25 ml) and 2N sodium hydroxide (10 ml) added. The solution was stirred at room temperature for 1 hour then poured into water and acidified with glacial acetic acid. The solution was extracted with dichloromethane (3 x 50 ml), and the combined extracts were dried over $MgSO_4$, filtered and evaporated to yield 3-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]propanoic acid.

b) [4-(2-Methylimidazo[4,5-c] pyrid-1-yl)phenyl]propanoic acid (1 mmol, 281 mg) was stirred in dichloromethane (10 ml) and one drop of dimethylformamide added. Oxalyl chloride (2 mmol, 254 mg) was added dropwise and the resulting solution stirred at room temperature for 30 minutes then evaporated to dryness. The residue was redissolved in dichloromethane (10 ml) and diethylamine (3 mmol, 219 mg) were added and the solution stirred for 30 minutes at room temperature. The reaction mixture was poured into water and extracted with dichloromethane (3 x 25 ml). The combined extracts were dried over Na_2SO_4, filtered and evaporated to dryness and the residue was purified by column chromatography on silica eluting with dichloromethane/methanol (97:3). The product containing fractions were evaporated to dryness and the oil crystallised from diethyl ether/hexane to give the title compound (194 mg, 58%), m.p. 123-125°C. Found: C,71.12; H,7.22; N,16.84. $C_{20}H_{24}N_4O$ requires C,71.43; H,7.14; N,16.67%.

EXAMPLES 57-60

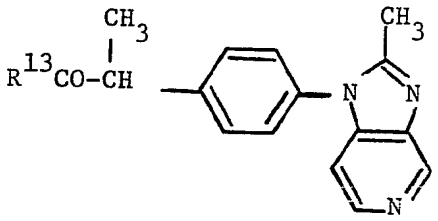
The following compounds were prepared as described in Example 56(b) above using the appropriate amine instead of diethylamine.

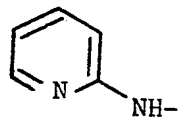
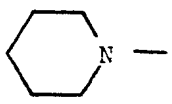


Example No.	R^{13}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
57		237-239	67.35 (67.37 (0.25 mole CH_2Cl_2)	5.13 5.15	18.59 18.49)
58	$(CH_3)_3CNH-$	171-173	70.93 (70.80 (0.17 mole H_2O)	7.25 7.26	16.33 16.52)
59		190-194	65.21 (65.02 (HCl, H_2O)	5.95 5.89	13.01 13.19)
60		155-157	68.24 (68.57	6.52 6.29	15.83 16.00)

EXAMPLES 61-64

Ethyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propanoate (Preparation 2) was hydrolysed following the procedure of Example 56 (a) and reacted with appropriate amines following the procedure of Example 56(b) to give the following compounds:



Example No.	R^{13}	m.p. °C	Analysis % (Theorectical in brackets) C	H	N
61	$(CH_3)_3CNH-$	165-167	71.45 (71.43	7.22 7.14	16.95 16.67)
62		100-104	70.34 (70.59	5.50 5.32	20.25 19.61)
63	$(C_2H_5)_2N-$	151-161	71.14 (71.43	7.26 7.14	16.33 16.67)
64		123-125	72.10 (72.41	7.03 6.90	16.52 16.09)

EXAMPLE 65

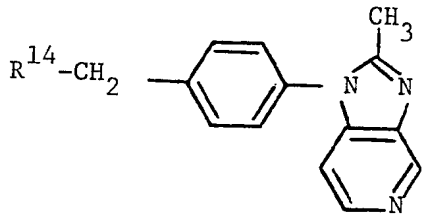
1-[4-(2,4-Difluorobenzylaminomethyl)phenyl]-2-methylimidazo[4,5-c]pyridine

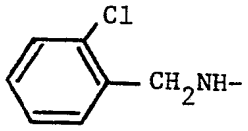
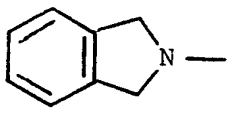
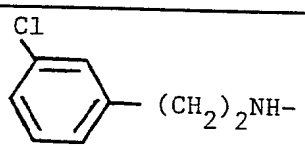
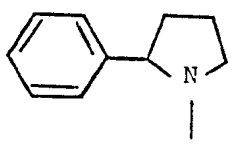
a) A suspension of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzaldehyde (750 mg, 3.16 mmol), 2,4-difluorobenzyl-amine (500 mg, 3.5 mmol) and silica gel (230-400 mesh) (1 g) in anhydrous dichloromethane (20 ml) was stirred for 16 hours at ambient temperature. The suspension was filtered, the filtrate evaporated to dryness and the residual gum triturated with anhydrous diethyl ether to afford the Schiff's base as white solid (700 mg, 61%).

b) Sodium borohydride (57 mg, 1.5 mmol) was added to a stirred solution of the above product (500 mg, 1.4 mmol) in anhydrous methanol (10 ml) at 0°C. The stirred solution was warmed to 20°C over 1 hour, then the solution concentrated, the residue acidified to pH 1 with 2M hydrochloric acid, water (20 ml) added and sodium bicarbonate added to pH 8. The solution was extracted with ethyl acetate (50 ml). The ethyl acetate extract was washed with water, dried over magnesium sulphate and concentrated to dryness. The residual gum was triturated with anhydrous diethyl ether to give the title compound as a white solid. (0.1 g, 20%), m.p. 108-110°C. Found: C,69.06, H,5.00; N,15.48. $C_{21}H_{18}F_2N_4$ requires C,69.22; H,4.98; N,15.37%.

EXAMPLES 66-69

The above procedure was followed using the appropriate amine in step (a) to yield the following products



Example No	R^{14}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
66		88-90	69.73 (69.51	5.28 5.28	15.58 15.44)
67		131-132	77.51 (77.62 (0.25 mole H_2O)	5.97 5.92	16.20 16.40)
68		104-106	69.26 (69.28	5.76 5.68	14.79 14.69)
69		foam	74.57 (74.58 (hydrate)	6.43 6.78	14.10 14.50)

EXAMPLE 70

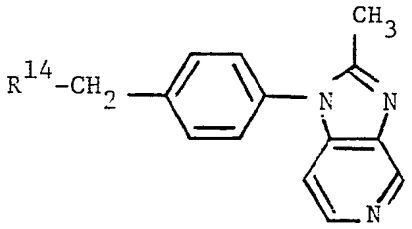
1-[4-(1,2,3,4-Tetrahydroisoquinolin-1-yl-methyl)phenyl]-2-methyl-imidazo[4,5-c]pyridine

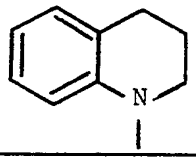
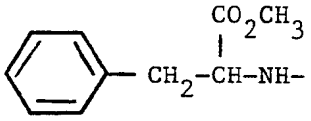
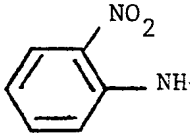
Glacial acetic acid was added to a stirred solution of 1,2,3,4-tetrahydroisoquinoline (3.50 g, 26.3 mmol) in anhydrous methanol (15 ml) until the pH was 7. 4-(2-Methylimidazo[4,5-c]-pyrid-1-yl)benzaldehyde (1.56 g, 6.6 mmol) was then added and the reactants stirred at ambient temperature for 20 minutes before adding sodium cyanoborohydride (0.63 g, 10 mmol). The reactants were stirred at ambient temperature for 20 minutes, then water (50 ml) added. 2M Hydrochloric acid was added to pH 2, followed by sodium bicarbonate to pH 8 and the aqueous solution was then extracted with dichloromethane (100 ml). The organic extract was washed with water (50 ml), dried over magnesium sulphate and concentrated under vacuum.

The residual gum was chromatographed on silica (230-400 mesh), eluting with 5% diethylamine in ethyl acetate. Appropriate fractions were combined and concentrated and the residual gum triturated with diethyl ether to give the title compound as a white solid (450 mg, 20%). M.p. 110 -112°C. Found: C,77.73; H,6.21; N,15.76. $C_{13}H_{22}N_4$ requires C,77.94; H,6.26; N,15.81%.

EXAMPLES 71-73

The following compounds were prepared by the above procedure using the appropriate amine instead of tetrahydroisoquinoline



Example No.	R^{14}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
71		140-142	77.83 (77.94)	6.22 (6.26)	16.11 (15.81)
72		gum	characterised by NMR(1)		
73		269-273	66.67 (66.84)	4.80 (4.77)	19.14 (19.49)

(1) δ ($CDCl_3$): 2.58(3H,s), 3.01(1H,dd J=11,6Hz), 3.10(1H,dd J=11, 6Hz), 3.60(1H,t J=6Hz), 3.74(3H,s), 3.78 and 3.98(each 1H,d J=15Hz), 7.08(1H,d J=4.5Hz), 7.2-7.4(8H,m), 7.47(2H,d J=8Hz), 8.41(1H,d J=4.5Hz) and 9.08(1H,s).

EXAMPLE 74

1-(4-N-Phthalimidomethylphenyl)-2-methylimidazo[4,5-c]pyridine

To a stirred suspension of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (431 mg, 1.8 mmol) in anhydrous tetrahydrofuran (10 ml) under nitrogen were added in turn, phthalimide (264 mg, 1.8 mmol), triphenylphosphine (471 mg, 1.8 mmol) and diethylazodicarboxylate (6.283 ml, 1.8 mmol). The solution was stirred at ambient temperature for 16 hours then evaporated to dryness and the residual gum chromatographed on silica (230-400 mesh), eluting with 10% - 20% methanol in ethyl acetate. Appropriate fractions were combined, concentrated and the residual gum triturated with ethyl acetate to give the title compound as a white solid (200 mg, 30%), m.p. 222-224°C. Found: C,71.44; H,4.42; N,15.22. $C_{22}H_{16}N_4O_2$ requires C,71.73; H,4.38; N,15.21%.

EXAMPLE 75

1-{4-[N-(2-Aminophenyl)aminomethyl]phenyl}-2-methylimidazo[4,5-c]-pyridine

Stannous chloride dihydrate (280 mg, 1.25 mmol) was added to a stirred solution of 2-methyl-1{4-[N-(2-nitrophenyl)amino-methyl]phenyl}-2-methylimidazo[4,5-c]pyridine (from Example 73) (90 mg, 0.25 mmol) in 2M hydrochloric acid (0.5 ml), ethanol (1 ml) and water (1 ml). The solution was stirred under reflux for 6 hours then cooled to ambient temperature and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate The organic extract was washed with water, dried over magnesium sulphate and concentrated to dryness. The residual gum was chromatographed on silica (230-400 mesh), eluting with 2%-10%

diethylamine in ethyl acetate. Appropriate fractions were combined, concentrated and the residual gum triturated with diethyl ether to give the title compound as an off-white solid (22 mg, 27%), m.p. 190-195°C. Found: C,71.99; H,5.88; N,20.28. $C_{20}H_{19}N_5 \cdot 0.125\ CH_3CO_2C_2H_5$ requires C,72.33; H,5.92; N,20.57%.

EXAMPLE 76

1-[4-Benzimidazol-1-ylmethyl)phenyl]-2-methylimidazo[4,5-c]-pyridine

A solution of 1-{4-[N-(2-aminophenyl)aminomethyl]phenyl}-2-methyl-imidazo[4,5-c]pyridine (300 mg, 0.91 mmol) and triethyl-orthoformate (5 ml, 30 mmol) in formic acid (0.5 ml) was stirred under reflux for 1 hour, then cooled to ambient temperature, diluted with water (50 ml) and stirred at ambient temperature for 16 hours. The solution was concentrated and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate (pH 8). The organic extract was separated, washed with water, dried over magnesium sulphate and concentrated to dryness. The residual gum was chromatographed on silica (230-400 mesh), eluting with 20% methanol in ethyl acetate. Appropriate fractions were combined and concentrated under high vacuum to give the title compound as a foam (150 mg, 49%). Found: C,73.57; H,5.06; N,20.16. $C_{21}H_{17}N_5 \cdot 1/4\ H_2O$ requires C,73.34; H,5.13; N,20.36%.

EXAMPLE 77

1-[4-(N-(2-Chlorobenzyl)-N-ethoxycarbonylamino)phenyl]-2-methyl-imidazo[4,5-c]pyridine

n-Butyl lithium (1.6M in hexane) (1.19 ml, 1.9 mmol) was added dropwise to a stirred solution of 1-[4-(2-chlorobenzyl-aminomethyl)phenyl]-2-methylimidazo[4,5-c]pyridine (0.61 g, 1.7 mmol) in anhydrous tetrahydrofuran, under nitrogen, at -30°C. After stirring for 20 minutes at -30°C, ethyl chloroformate (0.26 ml, 2.7 mmol) was added and the stirred reaction mixture warmed to ambient temperature over 16 hours. Saturated aqueous sodium bicarbonate solution was added to the stirred reaction mixture and the product extracted into ethyl acetate. The organic extract was washed with water, dried over magnesium sulphate and concentrated to an oil (700 mg). Chromatography on silica eluting with 5% methanol in ethyl acetate gave the title compound as a solid (90 mg, 11%), m.p. 118-122°C. Found: C,65.32; H,5.30; N,12.51. $C_{24}H_{23}ClN_4O_2.\frac{1}{2}H_2O$ requires C,64.93; H,5.45; N,12.62%.

EXAMPLE 78

1-[4-(N-Benzyl-N-ethoxycarbonylamino)phenyl]-2-methyl-imidazo[4,5-c]pyridine

This compound was prepared as described in the previous Example starting with the corresponding N-benzylaminomethyl derivative to give the title N-benzyl compound as a solid (37%). M.p. 129-132°C. Found: C,71.70; H,6.07; N,13.85. $C_{24}H_{24}N_4O_2$ requires C,71.98; H,6.04; N,13.99%.

EXAMPLE 79

N-(2-Chlorophenylacetyl)-4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylamine

a) Raney nickel (0.25 g) was added to a solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (2.34 g, 0.01 mmol) in acetic anhydride (15 ml) and the reaction mixture hydrogenated at 50°C and 50 p.s.i. (3.45 bar) for 1 hour. The reaction mixture was filtered, the filtrate diluted with water (5 ml) and concentrated hydrochloric acid (5 ml) and the solution stirred at 100°C for 16 hours. On cooling to ambient temperature, 2M sodium hydroxide was added to pH 9 and the product extracted with ethyl acetate. The organic extract was washed with water, dried over magnesium sulphate and concentrated under reduced pressure. Chromatography on silica, eluting with ethylacetate: methanol:diethylamine (90:5:5) gave 4-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzylamine. (0.6g, 25%).

b) Oxalyl chloride (0.7 ml, 8 mmol) was added to a stirred solution of 2-chlorophenylacetic acid (340 mg, 2 mmol) in anhydrous dichloromethane (6 ml) under nitrogen. Anhydrous dimethylformamide (2 drops) was added and the solution stirred at ambient temperature for 2 hours. The solution was concentrated under high vacuum, then re-dissolved in dichloromethane (10 ml) and a solution of 4-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzylamine (0.6 g, 2.5 mmol) in anhydrous dichloromethane (10 ml) added over 5 minutes. The solution was stirred at ambient temperature for 16 hours, then washed with saturated aqueous sodium carbonate (pH 9), dried over magnesium sulphate and concentrated under vacuum.

Chromatography on silica, eluting with 10% methanol in ethyl acetate gave the title compound as a foam (350 mg, 45%). Found: C,66.08; H,4.95; N,13.75. $C_{22}H_{19}ClN_4O.\frac{1}{2}H_2O$ requires C,66.08; H,5.04; N,14.01%.

EXAMPLE 80

N-(3',4'-Dichlorobenzoyl)amino-4-(2-methylimidazo[4,5-c]pyrid-1-yl acetophenone

a)Ethyl 4'-(2-methylimidazopyrid-1-yl)-2-oximinobenzoylacetate

A solution of sodium nitrite (3.3 g, 47 mmol) in water (40 ml) was added in drops to a solution of ethyl 4'-(2-methyl-imidazo[4,5-c]pyrid-1-yl)benzoylacetate (12.6 g, 39 mmol) in glacial acetic acid (45 ml) at 5°C. After 1.5 hours the mixture was partitioned between dichloromethane and brine. The organic layer was washed again with brine and then with saturated aqueous sodium bicarbonate, dried ($MgSO_4$) and evaporated to an oil which rapidly crystallised on addition of ether (9.61 g, 70%), (2:1 mixture of syn/anti isomers). M.p. 168-170°C.

b) Ethyl 2-acetamido-4'-(2-methylimidazo[4,5-c]pyrid-1-ylbenzoyl-acetate

A solution of the product from a) above (6 g, 17 mmol) in acetic acid (33 ml) and acetic anhydride (9 ml) was hydrogenated over 5% palladium on carbon (1 g) at 50 p.s.i. (3.45 bar) at 30°C for 2 hours. The mixture was filtered through a filter pad, washing the cake with methanol and the filtrate was evaporated. The residue was chromatographed eluting with methanol and then 10% methanol in ethyl acetate to afford a colourless foam (6.1 g, 94%). M.p. 71-73°C.

c) 2-Amino-4'-(2-methylimidazo[4,5-c]pyrid-1-yl)acetophenone dihydrochloride

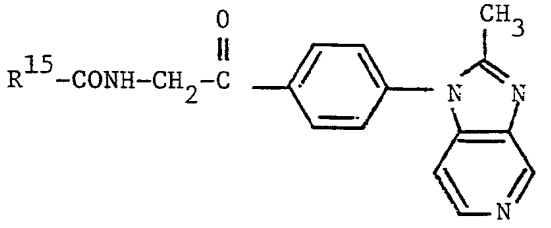
A solution of the product from b) above (1.2 g, 3.2 mmol) in 2M hydrochloric acid (30 ml) was heated at reflux for 3 hours. The solution was evaporated to dryness to yield the amine hydrochloride salt as a colourless foam (1.35 g), which was stored under vacuum.

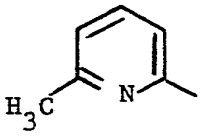
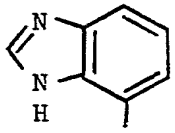
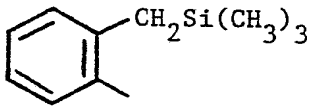
d) N-(3',4'-Dichlorobenzoyl)amino-4-(2-methylimidazo[4,5-c]pyrid-1-yl acetophenone

N-Methylmorpholine (1.6 ml, 16 mmol) was added to a stirred suspension of the product from c) above (0.7 g, 1.8 mmol), 1-hydroxybenzotriazole (0.34 g, 2.4 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (0.89 g, 4.7 mmol) and 3,4-dichlorobenzoic acid (0.42 g, 2.2 mmol) in dichloromethane (25 ml). After 26 hours, the mixture was evaporated and partitioned between water and ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to an orange gum (0.69 g). Chromatography, eluting with 15% methanol in ethyl acetate, afforded a foam which solidified upon trituration with diethyl ether, (0.3 g, 38°%), m.p. 108-110°C. Found: C,58.78; H,3.76; N,12.20%. $C_{22}H_{16}Cl_2N_4O_2.\frac{1}{2}H_2O$ requires C,58.93; H,3.83; N,12.50%.

EXAMPLES 81-83

The following compounds were prepared as described in the previous Example using the appropriate acid in step d):



Example No	R^{15}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
81		148-150	67.82 (67.78 (0.25 mole H_2O)	4.88 4.98	17.57 17.96)
82		229-230	characterised by NMR (1)		
83		197-200	characterised by NMR (2)		

(1) δ (DMSO-d_6) 2.56(3H,s), 5.16(2H,d J=5Hz) 7.28(1H,d J=5.5Hz), 7.38(1H,t J=8Hz), 7.80(3H,m), 7.91(1H,d J=7Hz), 8.31(3H,m), 8.55 and 8.94(each 1H,s), 10.43 (1H,t J=5Hz), and 13.08 (1H,s).

(2) ($CDCl_3$) 0.05(9H,s), 2.56(2H,s), 2.64(3H,s) 5.04(2H,d, J=5Hz), 6.90 br(1H,t), 7.15(3H,m), 7.38(1H,t, J=7Hz), 7.54(1H,d, J=7Hz), 7.60(2H,dJ=9Hz), 8.32(2H,d J=9Hz), 8.45(1H,d J=5Hz) and 9.12(1H,s).

EXAMPLE 84

N-(2-Methylbenzoyl)amino-4-(2-methylimidazo[4,5-c]pyrid-1-yl)-acetophenone

Sodium methoxide (284 mg, 5.26 mmol) was added to a stirred solution of N-(2-trimethylsilylmethylbenzoyl)-4-(2-methyl-imidazo[4,5-c]pyrid- 1-yl)aminoacetophenone (from Example 83 above) (1.2 g, 2.63 mmol) in anhydrous dimethylformamide (10 ml) under nitrogen. The solution was stirred at 100°C for 30 minutes, then concentrated to dryness. The residue was dissolved in ethyl acetate (50 ml), washed with water (3 x 50 ml), dried over magnesium sulphate and concentrated under reduced pressure. Chromatography on silica (230-400 mesh), eluting with 15% methanol in ethyl acetate, and trituration with diethyl ether gave the title compound as a hygroscopic white solid (200 mg, 20%). ^{1}H NMR ($CDCl_3$): 2.56(3H,s); 2.64(3H,s); 5.04(2H,d, J=5Hz); 6.90(1H,broad); 7.17(1H,d,J=5Hz); 7.28(3H,m); 7.58(1H,d,J=7Hz); 7.60(2H,d,J=9Hz); 8.32(2H,d,J=9Hz); 8.45(1H,d,J=5Hz); 9.12(1H,s).

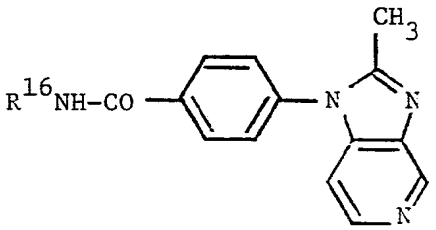
EXAMPLE 85

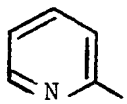
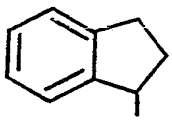
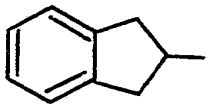
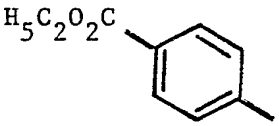
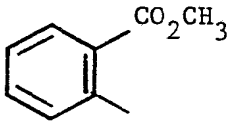
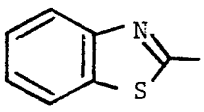
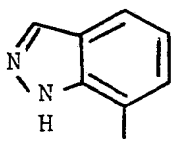
4-(2-Methylimidazo[4,5-c]pyrid-1-yl)-N-(3-quinolinyl)benzamide

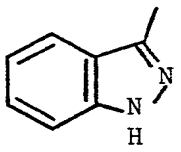
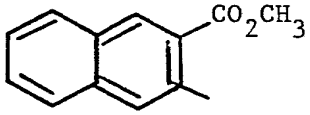
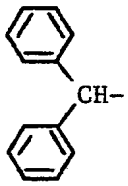
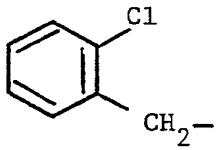
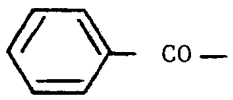
Oxalyl chloride (508 mg, 40 mmol) was added dropwise to a stirred suspension of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoic acid (253 mg, 1.0 mmol) in dry dichloromethane (4 ml) at 0°C under nitrogen. After the addition was complete, the suspension was sonicated at room temperature for 1 hour. The solvent was then evaporated under reduced pressure to give an off-white solid, which was resuspended in dry dichloromethane (4 ml) and a solution

of 3-amino-quinoline (288 mg, 2.0 mmol) and triethylamine (505 mg, 5.0 mmol) in dry dichloromethane (2 ml) was added dropwise. The resulting mixture was sonicated for 1 hour at room temperature, and then treated with saturated aqueous sodium bicarbonate (20 ml). The mixture was extracted with dichloromethane (3 x 30 ml) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with dichloromethane/methanol. Fractions containing product were combined, concentrated and triturated with a little ether to give the title compound, as a white solid, m.p. 259-261°C. Found: C,72.56; H,5.45; N,18.13. $C_{23}H_{17}N_{50}$ requires C,72.80; H,4.52; N,18.46%.

The following compounds shown in the Table were prepared by a similar method substituting the corresponding amine for 3-aminoquinoline.



Example No	R^{16}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
86		221-223	68.86 (69.28	4.58 4.59	21.01 21.27)
87		238-239	74.99 (74.98	5.57 5.47	15.40 15.21)
88		218-220	75.02 (74.98	5.36 5.47	15.12 15.21)
89		193-195	68.92 (68.98	5.07 5.03	13.80 13.99)
90		220-222	68.35 (68.38	4.72 4.70	14.40 14.50)
91		309-312	63.47 (63.45 (0.67 mole H_2O)	4.04 4.14	17.80 17.62)
92		269-271	67.63 (67.64 (0.25 mole H_2O)	4.37 4.46	22.83 22.54)

Example No	R^{16}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
93		280-283	66.86 (66.83 (0.5 mole H_2O)	4.33 4.54	21.96 22.27)
94		193-196	characterised by NMR (1)		
95		213-215	76.02 (76.39 (0.33 mole H_2O)	5.36 5.38	13.07 13.20)
96		94-97	66.55 (66.93	4.88 4.55	14.88 14.87)
97		153-155	66.21 (66.30 (0.5 mole H_2O)	4.58 4.77	18.38 18.41)

(1) δ (300MHz, $CDCl_3$) 2.64(3H,s), 4.11(3H,s), 7.20(1H,d,J=5Hz), 7.48(1H,t,J=7Hz), 7.60(2H,d,J=8Hz), 7.65(1H,t,J=7Hz), 7.92(1H,d,J=8Hz), 7.95(1H,d,J=8Hz), 8.38(2H,d,J=8Hz), 8.46(1H,d,J=5Hz), 8.79(1H,s), 9.13(1H,s), 9.44(1H,s).

EXAMPLE 98

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoylbenzo[c]pyrroline

Sodium hydride (60% oil dispersion, 0.2 g, 5 mmol) was added to a stirred solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzamide (0.5 g, 2 mmol) in tetrahydrofuran (5 ml) and dimethylformamide (5 ml). After warming at 50°C for 20 minutes, 1,2-bis-bromomethylbenzene (0.53 g, 2 mmol) was added. After 2 hours at 25°C, the solvents were evaporated and the residue was partitioned between aqueous sodium bicarbonate and ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to a residue which was purified by flash chromatography, eluting with 5% diethylamine in ethyl acetate, to afford a white solid (0.038 g, 7%), m.p. 226-229°C. Found: C,72.79; H,5.14; N,15.12. $C_{22}H_{18}N_4O.\frac{1}{2}H_2O$ requires C,72.71; H,5.27; N,15.41%.

EXAMPLE 99

N,N-Bis(2-Chlorobenzyl)-4-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzamide

Sodium hydride (60% dispersion in mineral oil), (44 mg, 1.1 mmol) was added to a stirred solution of 4-(2-methylimidazo-[4,5-c]-pyrid-1-yl)-benzamide (252 mg, 1 mmol), in anhydrous tetrahydrofuran (1 ml) and anhydrous dimethylformamide (1 ml). The solution was stirred at 50°C for an additional 20 minutes before adding a solution of 2-chlorobenzylchloride (177 mg, 1.1 mmol) in anhydrous tetrahydrofuran (1 ml). The reaction mixture was stirred at ambient temperature for 16 hours, then diluted with water, 2M hydrochloric acid added to pH 1, followed by sodium bicarbonate to give pH 8 and the product was extracted

with ethyl acetate. The organic extract was washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residual gum was chromatographed on silica eluting with 15% methanol in ethyl acetate. The faster running (less polar) of the two ensuing fractions was concentrated and the residual gum crystallised with ether in an ultrasonic bath to give the title compound as a white solid (8 mg, 2%), m.p. 176-180°C. Found: C,66.36; H,4.42; N,11.10. $C_{28}H_{22}Cl_2N_4O$. 0.33 H_2O requires C,65.59; H,4.46; N,10.93%.

EXAMPLE 100

Methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoate

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (7.78 mmol, 1.86 g), methyl thiosalicylate (8.56 mmol, 1.44 g) and triphenylphosphine (18.56 mmol, 2.24 g) were dissolved in dry tetrahydrofuran (30 ml). Diethylazodicarboxylate (9.34 mmol, 1.95 g) was added dropwise and the mixture stirred for 2 hours at room temperature then evaporated to dryness. The residue was purified by column chromatography on silica eluting with dichloromethane/ methanol (97:3). The oily product was dissolved in dichloromethane and treated with anhydrous HCl. The hydrochloride crystallised on standing (1.66 g, 50%) M.p. 249-253°C. Found: C,60.12; H,4.67; N,9.57. $C_{22}H_{19}N_3O_2S$. HCl:0.75 H_2O requires C,60.14; H,4.90; N,9.57%.

EXAMPLE 101

Methyl 4-chloro-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyl-thio]benzoate

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (7.4 mmol, 1.76 g) was dissolved in 48% hydrobromic acid (25 ml) and heated under reflux for 15 minutes then evaporated to dryness under vacuum. The residue was dissolved in methanol (100 ml) and methyl 4-chloro-thiosalicylate (10 mmol, 2.03 g) added. Sodium hydrogen carbonate (25 mmol, 2.10 g) was added portionwise and the mixture stirred overnight. The resulting suspension was poured into ethyl acetate and washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness. The residue was chromatographed on silica eluting with methanol, dichloromethane (97:3) to give the pure product. This was redissolved in dichloromethane and treated with ethanolic hydrogen chloride. The solution was evaporated to dryness and the residue recrystallised from ethyl acetate/methanol to give the hydrochloride salt (3.69 g, 95%), m.p. 233-255°C. Found: C,56.82; H,4.39; N,8.87. $C_{22}H_{18}ClN_3O_2S.HCl.0.25\ H_2O$ requires C,56.84; H,4.20; N,9.04%.

EXAMPLE 102

1-[4-(2-Chlorophenylthiomethyl)phenyl]-2-methyl-imidazo[4,5-c]-pyridine

The above compound was made following the procedure of Example 101 using 2-chloro-benzenethiol as starting material. M.p. 278-280°C. Found: C,58.75; H,4.31; N,10.38. $C_{20}H_{16}ClN_3S.HCl.\ 0.25\ H_2O$ requires C,59.04; H,4.31; N,10.33%.

EXAMPLE 103

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoic acid

Methyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoate (2.5 mmol, 1 g) was dissolved in ethanol (20 ml) and 2N sodium hydroxide (15 ml) was added. The mixture was stirred overnight then poured onto water and washed with dichloromethane. The aqueous phase was acidified with acetic acid and re-extracted with dichloromethane (3 x 75 ml). The combined extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The resulting white solid was washed with ether. (0.81 g, 86%). M.p. 251-254°C. Found: C,65.95; H,4.68; N,10.71. $C_{21}H_{17}N_3O_2S$ 0.5 H_2O requires C,65.63; H,4.69; N,10.94%.

EXAMPLE 104

4-Chloro-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoic acid

The above Example was followed using the compound of Example 101 to give the title product in 78% yield. M.p. 264-267°C. Found: C,61.31; H,3.95; N,10.11. $C_{21}H_{16}N_3ClO_2S$ requires C,61.54; H,3.91; N,10.26%.

EXAMPLE 105

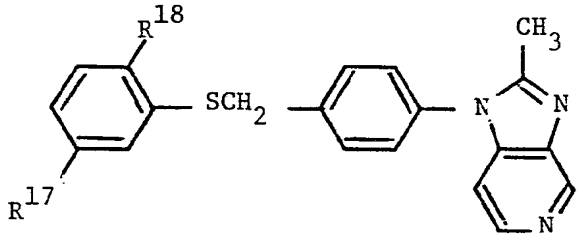
N-Methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]-benzamide

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoic acid (1 mmol, 375 mg) was stirred in dichloromethane (10 ml) and 1 drop of dimethylformamide was added. Oxalyl chloride (2 mmol, 254 mg) was added and the mixture stirred for 90 minutes under

nitrogen. The solvent was removed under vacuum and the residue dissolved in dichloromethane (10 ml) and added dropwise to an ice cold solution of methylamine (33% solution in ethanol 10 ml). The mixture was stirred at 0°C for 30 minutes then poured into water and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried over Na_2SO_4, filtered and evaporated to dryness. Purification was effected by column chromatography on silica eluting with dichloromethane/methanol (97:3). The product containing fractions were evaporated to dryness and crystallised on trituration with ether. (0.28 g, 73%). M.p. 172-174°C. Found: C,67.26; H,5.25; N,13.92. $C_{22}H_{20}N_4OS$. 0.25 H_2O requires C,67.26; H,5.22; N,14.27%.

EXAMPLES 106-107

The following compounds were prepared as described in the previous Example using the appropriate acid and reacting with dimethylamine.



Example No	R^{17}	R^{18}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
106	H	$-CON(CH_3)_2$	178-180	68.17 (67.90 (0.25 mole H_2O)	5.53 5.54	13.60 13.78
107	Cl	$-CON(CH_3)_2$	136-139	58.38 (58.03 (HCl, 0.5 mole $C_4H_8O_2$)	5.08 5.03	10.82 10.83)

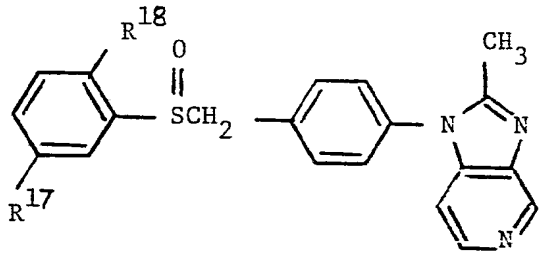
EXAMPLE 108

Methyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]benzoate-S-oxide

Methyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]-benzoate (1 mmol, 389 mg) was dissolved in dichloromethane (15 ml) and cooled in an ice bath, m-chloroperbenzoic acid (85% 1 mmol, 203 mg) was added and the solution stirred for 2 hours then poured into dilute sodium hydrogen carbonate solution and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness, the residue being purified by column chromatography on silica eluting with dichloromethane/methanol (97:3). The product-containing fractions were evaporated to dryness and the residue re-crystallised from dichloromethane. (0.33 g, 81%). M.p. 146-148°C. Found: C,64.79; H,4.74; N,10.24. $C_{22}H_{19}N_3O_3S$ requires C,65.19; H,4.69; N,10.37%.

EXAMPLES 109-112

Oxidation of the appropriate thio compound of Examples 102-107 with meta-chloroperbenzoic acid as described in the previous example gave the following sulphoxides:



Example No	R^{17}	R^{18}	m.p. °C	Analysis % (Theoretical in brackets) C	H	N
109	H	$-CONHCH_3$	205-207	64.46 (64.39 (0.33 mole H_2O)	5.11 5.04	13.46 13.66)
110	H	$-CON(CH_3)_2$	183-185	66.01 (66.03	5.58 5.26	13.22 13.40)
111	H	Cl	120-122	62.67 (62.91	4.18 4.19	10.86 11.01)
112	Cl	$-CON(CH_3)_2$	159-161	60.94 (60.99	4.66 4.64	12.23 12.38)

EXAMPLE 113

N-Methyl-2-[4-(2-methylimidazo-[4,5-c]pyrid-1-ylbenzylthio]benzamide-S,S-dioxide

N-Methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylthio]-benzamide-S-oxide (0.25 mmol, 101 mg) was dissolved in dichloromethane (10 ml) and cooled in an ice bath. Concentrated hydrochloric acid (5 drops) was added followed by m-chloroperbenzoic acid (85%, 0.25 mmol, 51 mg) and the mixture stirred at 0°C for 2 hours then at room temperature for 2 hours. The mixture was basified with 5% sodium carbonate solution and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried over Na_2SO_4, filtered and evaporated to dryness with the residue being purified by column chromatography on silica eluting with dichloromethane/methanol (96:4). Evaporation of the product-containing fractions gave an oil which crystallised on trituration with ether, (14 mg, 13%). M.p. 241-243°C. Found: C,61.91; H,4.75; N,12.79. $C_{22}H_{20}N_4O_3S$. 0.33 H_2O requires C,61.97; H,4.85; N,13.14%.

EXAMPLE 114

N,N-Dimethyl-4-chloro-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl-benzylthio]benzamide-S,S-dioxide

The above procedure was followed starting with the corresponding 4-chloro-derivative to give the title product. M.p. 193-194°C; Found: C,57.81; H,4.48; N,11.50. $C_{23}H_{21}ClN_4O_3S$. 0.5 H_2O requires C,57.80; H,4.61; N,11.73%.

EXAMPLE 115

1-[(2-Dimethylaminocarbonyl)phenylsulphinyl]-1-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]methanol

N,N-Dimethyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyl-thio]benzamide-S-oxide (0.3 mmol, 125 mg) was dissolved in dry dichloromethane (110 ml) and anhydrous hydrogen chloride added. m-Chloroperbenzoic acid (85%, 0.3 mmol, 61 mg) was added and the mixture stirred at room temperature for 2 hours then poured into 5% sodium carbonate solution and extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by high pressure liquid chromatography and the product crystallised from diethyl ether (17 mg, 13%). M.p. 174-176°C. Found: C,60.90; H,4.70; N,12.14. $C_{23}H_{22}N_4O_3S.\ H_2O$ requires C,61.06; H,5.30; N,12.39%.

EXAMPLE 116

Dimethyl 2-(4,5-dichloro-2-nitrophenyl)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethyl malonate

a) Following the method of W. Lehrest, Tetrahedron 1973, 29, 635, titanium tetrachloride (4.40 ml, 40 mmol) was added at 5-10°C to dry tetrahydrofuran (80 ml) under nitrogen. Dimethyl malonate (2.64 g, 20 mmol) was added by syringe, followed by a solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde (4.74 g, 20 mmol)

in dry tetrahydrofuran (80 ml). Finally dry pyridine (4.85 ml, 60 mmol) was added dropwise and the resulting suspension was stirred at room temperature for 24 hours. Methanol (30 ml) was added, and the resulting white suspension was poured into a mixture of dichloromethane (100 ml), ice, and saturated aqueous sodium bicarbonate (500 ml). The titanium salts were removed by filtration, and washed with dichloromethane. The filtrate layers were separated, and the aqueous layer extracted with dichloromethane (2 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. On the addition of diethyl ether (50 ml), the product crystallised, and was filtered off and dried, to afford dimethyl 4'(2-methylimidazo-[4,5-c]pyrid-1-yl)benzylidene malonate, as a white solid, 5.1 g 73%). A portion was recrystallised from hot ethyl acetate. M.p. 155-156°C. Found: C,64.79; H,4.95; N,11.87. $C_{19}H_{17}N_3O$ requires C,64.95; H,4.88; N,11.96%.

(b) A solution of 4,5-dichloro-2-nitrotoluene (2.472 g, 12.0 mmol) in dry dimethylformamide (5 ml) was added over 2 minutes by syringe to a suspension of sodium hydride (600 mg, 60% dispersion in oil, 15.0 mmol) and dimethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)benzylidene malonate (from part a) in dry dimethylformamide (40 ml) whilst maintaining the temperature below 15°C. The resulting brown solution was stirred at 20°C for 3 hours, and glacial acetic acid (2 ml) was added. The mixture was poured into ethyl acetate (400 ml) and the solution rendered basic by the addition of saturated aqueous sodium bicarbonate. The organic layer was washed with water (3 x 100 ml), brine (100 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by chromatography, eluting with a gradient of ethyl acetate/methanol, to give the title compound as a white solid, (3.119 g, 56%), m.p. 94-96°C (methanol). Found: C,53.18; H,4.30; N,9.51. $C_{26}H_{22}Cl_2N_4O_6 \cdot 1.5\ H_2O$ requires C,53.43; H,4.31; N,9.59%.

EXAMPLE 117

Dimethyl 2-(2-amino-4,5-dichlorophenyl)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethylmalonate

A solution of 25% aqueous titanium trichloride (4 ml, 6.5 mmol) was added dropwise to a solution of dimethyl 2-(4,5-dichloro-2-nitro-phenyl)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethylmalonate (557 mg, 1.0 mmol) in degassed methanol (15 ml) under nitrogen at room temperature. The solution was stirred for 1 hour, poured into dichloromethane (50 ml) and rendered basic by the addition of saturated aqueous sodium

bicarbonate. The precipitated salts were filtered off and washed with dichloromethane (150 ml). The filtrate was separated, dried ($MgSO_4$) and concentrated under reduced pressure to the give the title compound as a white solid, (452 mg, 86%), m.p. 186-188°C (methanol). ^1H NMR (300 MHz, $CDCl_3$) : 2.52(3H,s), 2.59(1H,d,J 12Hz), 3.15(1H,dd,J 12 and 2Hz), 3.55(3H,s), 3.70(1H,dt, J 12 and 2Hz), 3.91(3H,s), 3.96(1H,d,J 12Hz), 4.44(2H,br s), 6.25(1H,s), 6.78(1H,s), 7.03(1H,d, J 6Hz), 7.29 (4H,s), 8.39(1H,d,J 6Hz), 9.07(1H,s).

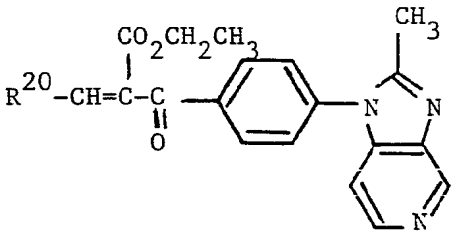
EXAMPLE 118

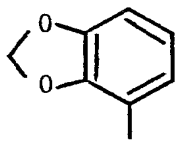
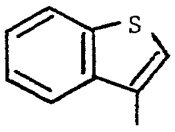
3-(2-Chlorophenyl)-2-ethoxycarbonyl-1-[4-(2-methylimidazo[4,5-c]-pyrid-1-yl)phenyl]prop-2-ene-1-one

A mixture of 2-chlorobenzaldehyde (2.8 g, 19.9 mmol), ethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoyl acetate (6.4 g, 19.9 mmol) and piperidine (100 microlitres) were stirred at room temperature for 48 hours in acetonitrile (30 ml). The mixture was evaporated to dryness and the residue chromatographed on silica eluting with ethyl-acetate/methanol (5:1). The fractions containing product were combined and evaporated to give the title compound (5.3 g, 60%). ^1H NMR ($CDCl_3$): 1.35(3H, t,J 8Hz), 2.53(3H, s), 4.27(2H, q,J 8Hz), 7-9.1(12H, m).

EXAMPLES 119-120

The following compounds were made by the method of Example 118 using the appropriate aromatic aldehyde as starting material.



Example No	R^{20}	N.M.R data ($CDCl_3$)
119		1.38(3H,t,J=8); 2.6(3H,s); 4.32(2H,q,J=8); 6.02(2H,s); 6.7-9.1(11H,m)
120		1.31(3H,t,J=8); 2.58(3H,s); 4.28(2H,q,J=8); 7.1-9.1(13H,m).

EXAMPLE 121

Ethyl 2-(2-chlorophenylmethyl)-3-hydroxy-3-[4-(2-methylimidazo-[4,5-c]pyrid-1-yl)phenyl]propanoate

Sodium borohydride (0.012 g) was added in a single portion to a solution of 3-(2-chlorophenyl)-2-ethoxycarbonyl-1-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]prop-2-ene-1-one (0.13 g, 0.3 mmol) in ethanol (2 ml) at 20°C. After 1 hour, the mixture was partitioned between ethyl acetate and brine. The organic layer was dried ($MgSO_4$) and evaporated to a gum. Purification by chromatography on silica afforded a colourless gum (0.12 g, 91%). Found: C,61.79; H,5.41; N,8.93. $C_{25}H_{24}ClN_3O_3.2\ H_2O$ requires C,61.79; H,5.81; N,8.65%.

EXAMPLE 122

2-Chlorobenzyl 2-(2-chlorophenylmethylidene)-3-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]-3-oxopropanoate

a) 2-Chlorobenzyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoyl-acetate

A solution of ethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoylacetate (1 g, 3 mmol) and 2-chlorobenzyl alcohol (1.4 g, 10 mmol) in toluene (15 ml) was heated at reflux for 20 hours, then cooled and evaporated. The residue was purified by chromatography to afford a colourless foam (1.23g, 95%).

Found: C,64.15; H,4.38; N,9.55. $C_{23}H_{18}ClN_3O_3.\ 0.5\ H_2O$ requires: C,64.41; H,4.47; N,9.80%.

b) Piperidine (0.02 ml) was added to a stirred solution of the product from a) (0.7 g, 1.67 mmol) and 2-chlorobenzaldehyde (0.28 g, 2 mmol) in acetonitrile (8 ml) at 22°C. The mixture was allowed

to stand for 62 hours, then evaporated and purified by chromatography to give the title compound as a colourless foam (0.39 g, 43%), m.p. 59-61°C. Found: C,65.55; H,4.10; N,7.40. $C_{30}H_{21}Cl_2N_3O_3 \cdot 0.5\ H_2O$ requires C,65.35; H,4.02; N,7.62%.

EXAMPLE 123

3-(2-Chlorophenyl)-1-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-1-oxo-2-propene

Solid sodium hydroxide (0.04 g, 1 mmol) was added to a stirred solution of 2-chlorobenzaldehyde (0.194 g, 1.4 mmol) and 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)acetophenone (0.35 g, 1.4 mmol) in methanol at 25°C. Water (2-3 drops) was added to aid dissolution. After 2 hours, the pH was adjusted to 8 by addition of 2M hydrochloric acid followed by sodium bicarbonate solution, then the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated to a gum. Flash chromatography, eluting with 10% methanol in ethyl acetate, afforded a solid which was recrystallised from methanol to give the title compound (0.08 g, 16%), m.p. 155-157°C. Found: C,70.67; H,4.22; N,11.12. $C_{22}H_{16}ClN_3O$ requires: C,70.68; H,4.31; N,11.24%.

EXAMPLE 124

E and Z-1-Phenyl-2-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-ethene

Sodium methoxide (0.11 g, 2 mmol) was added to a stirred solution of 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde (0.24 g, 1 mmol) and benzyltriphenylphosphonium chloride (0.43 g,

1.1 mmol) in anhydrous dimethylformamide (5 ml). After 18 hours at 23°C the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic extract was washed three times with water, dried ($MgSO_4$) and evaporated to a gum. Flash chromatography eluting with 5% methanol in ethyl acetate, afforded an amorphous solid (0.13 g, 44%). (Ratio of E/Z isomers was approximately 9:1)

^1H NMR ($CDCl_3$): 2.57(3H,s) 6.68 and 6.81 (each 1H,d J=14Hz), 7.13(1H,d J=4.5Hz), 7.23(2H,d J=8Hz), 7.34(5H,brs), 7.49(2H,d J=8Hz), 8.42(1H,d J=4.5Hz) and 9.07(1H,s).

EXAMPLE 125

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-pyrid-2-yl ethanol

Sodium methoxide (0.33 g, 6 mmol) was added to a stirred solution of 2-(trimethylsilylmethyl)pyridine (0.55 g, 3.3 mmol) and 4'-(2-methylimidazo[4,5-c]pyrid-1-yl-benzaldehyde (0.71 g, 3 mmol) in dry dimethylformamide (10 ml) under nitrogen. After 30 minutes, most of the solvent was removed and the residue partitioned between ethyl acetate and water. The organic layer was washed several times with water then dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography, eluting with 20% methanol in ethyl acetate, followed by trituration with ether, gave a white solid (0.1 g, 11%). M.p. 160-162°C. Found: C,72.23; H,5.46; N,16.69. $C_{20}H_{18}N_4O$. 0.125 H_2O requires C,72.21; H,5.53; N,18.84%.

EXAMPLE 126

E and Z-1-(2-Cyanophenyl)-2-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]ethane

Sodium methoxide (4.32 g, 80 mmol) was added to a stirred suspension of 2-chlorobenzyltriphenylphosphonium bromide (20.2 g, 44 mmol) and 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde (9.5 g, 40 mmol) in dimethylformamide (210 ml). The mixture was heated to 100°C for 3 hours then evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated to a gum (20 g) which was chromatographed on silica eluting with a gradient of from 5% to 25% methanol in ethyl acetate, to afford two products:

a) E-isomer, colourless foam (0.5 g, 4%).

^1H NMR (CD_3SOCD_3): 2.46(3H,s), 6.91 and 7.05 (each 1H,d J=15Hz), 7.15(1H,d J=5Hz) 7.33(2H,d J=7.5Hz), 7.49(4H,m), 7.66(1H,t J=7.5Hz), 7.90 (1H,d J=7.5Hz), 8.28(1H,d J=5Hz) and 8.89(1H,s).

b) Z-isomer, recrystallised from toluene (7 g, 52%). M.p. 213-215°C.

^1H NMR (CD_3SOCD_3): 2.51(3H,s), 7.25(1H,d J=5Hz), 7.50(2H,m), 7.67(3H,m), 7.75(1H,t J=7.5Hz), 7.91 (3H,m), 8.07(1H,d J=7.5Hz), 8.30(1H,d J=5Hz) and 8.92 (1H,s).

EXAMPLE 127

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1-oxo-2,2,3,3,4,4,4-heptafluorobutane

To a solution of heptafluoropropyliodide (60 mmol, 17.76 g) in ether (200 ml) was added phenylmagnesium bromide (55 mmol 18.33 ml) (3M in ether) whilst keeping the internal temperature below -60°C. The mixture was then stirred at -70°C for 15 minutes

followed by the dropwise addition of ethyl [4-(2-methylimidazo-[4,5-c]pyrid-1-yl)benzoate (25 mmol, 7.05 g) in tetrahydrofuran (40 ml) again keeping the temperature below -60°C. The mixture was allowed to warm to 0°C very slowly over a 5 hour period then quenched with ammonium chloride solution. After pouring the mixture into water the product was extracted into ethyl acetate (2 x 300 ml) and the combined organic extracts dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography on silica eluting with dichloromethane/ methanol (95:5) then recrystallised from ethyl acetate/hexane. (5.41 g, 53%). M.p. 138-141°C. Found: C,41.10; H,2.74; N,10.01. $C_{17}H_{10}F_7N_3O$ 0.5 H_2O requires C,49.29; H,2.68; N,10.14%.

EXAMPLE 128

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,2,3,3,4,4,4-heptafluoro-1-[4-fluorophenyl]butanol

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1-oxo-2,2,3,3,4,4,4-heptafluorobutane (1 mmol, 405 mg) was dissolved in tetrahydrofuran (10 ml) and cooled to -40°C. 4-Fluorophenyl-magnesium bromide (5 mmol, 5 ml, 1M in tetrahydrofuran) was added dropwise and the solution allowed to warm to room temperature over 1 hour and then stirred for a further 2 hours at room temperature. The reaction was quenched with ammonium chloride solution and poured into water (100 ml) then extracted with ethylacetate (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by chromatography on silica eluting with ethyl acetate/diethylamine

(98:2), the product containing fractions were evaporated to dryness and the residue recrystallised from ether (134 mg, 27%). M.p. 192-194°C. Found: C,54.77; H,3.31; N,8.37. $C_{23}H_{15}F_8N_3O$ requires C,55.09; H,2.99; N,8.38%.

EXAMPLE 129

4-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-tetradecafluoro-heptan-4-ol

The above was prepared analogously to the previous method using heptafluoropropyl magnesium bromide as the Grignard reagent and was obtained in 5% yield. M.p. 221-223°C. Found: C,41.74; H,1.91; N,7.30. $C_{20}H_{11}F_{14}N_3O$ requires C,41.44; H,2.11; N,7.30%.

EXAMPLE 130

4-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,1,1,2,2,3,3-heptafluoropentan-2-ol

The above was prepared analogously to the previous method using methylmagnesium bromide as the Grignard reagent to give the produce in 56% yield. M.p. 233-235°C. Found: C,51.15; H,3.31; N,9.82. $C_8H_{14}F_7N_3O$ requires C,51.31; H,3.33; N,9.98%.

EXAMPLE 131

3-Heptafluoropropyl-3-hydroxy-3-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propionamide

Bis(trimethylsilyl)acetamide (5 mmol, 1.24 ml) was dissolved in tetrahydrofuran (15 ml) and cooled to -78°C in a CO_2/acetone bath. Butyllithium (2.2M, in hexane, 5 mmol, 2.27 ml) was added dropwise over 5 minutes and the solution stirred at -78°C for a

further 15 minutes. A solution of 1-[4-(2-methylimidazo[4,5-c]-pyrid-1-yl)phenyl]-1-oxo-2,2,3,3,4,4,4-heptafluorobutane (1 mmol 405 mg) freshly dried by evaporation of a toluene solution was dissolved in tetrahydrofuran (15 ml) and added dropwise to the anion solution over 20 minutes. The mixture was stirred at -78°C for 1½ hours then the cooling bath removed and the mixture quenched with ammonium chloride solution. The reaction mixture was poured in water (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. Chromatography on silica followed by recrystallisation from ethyl acetate/ether gave the title product (145 mg, 31%), m.p. 233-239°C dec. Found: C,48.93; H,3.31; N,12.00. $C_{19}H_{15}F_7N_4O_2$ requires C,49.14; H,3.23; N,12.07%.

EXAMPLE 132

1-Heptafluoropropyl-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl-2-[1,2,4-triazol-1-yl]ethanol

a) 1-Heptafluoropropyl-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]oxirane

1-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1-oxo-2,2,3,3,4,4,4-heptafluorobutane (6 mmol, 2.43 g) was dissolved in tetrahydrofuran (30 ml) and cooled in an ice bath. Dimethylsulphoxonium methylide (0.6 M in tetrahydrofuran, 10 mmol, 16.7 ml) was added dropwise and the solution stirred at 0°C for 20 minutes. The reaction mixture was then poured into brine and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to

dryness. The residue was purified by column chromatography on silica eluting with dichloromethane/methanol (97:3) to give the oxirane as an unstable oil which was used immediately.

b) 1-Heptafluoropropyl-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl) phenyloxirane (0.6 mmol, 250 mg) and sodium triazole (1 mmol, 93 mg) were stirred in dimethylformamide (5 ml) for 40 minutes at room temperature. The reaction mixture was poured into brine and extracted with ethyl acetate (3 x 50 ml). The combined extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by column chromatography eluting with dichloromethane/methanol (94:6). The product containing fractions were evaporated to dryness and triturated with ether to give the title product (80 mg, 27%), m.p. 211-213°C. Found: C,48.39; H,3.26; N,16.40. $C_{20}H_{15}F_7N_6O$, 0.1 $(C_2H_5)_2O$, 0.5 H_2O requires C,48.53; H,3.37; N,16.65%.

EXAMPLE 133

2-Cyano-1-heptafluoropropyl-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]ethanol

The above was prepared in a similar manner to the previous example, but reacting the oxirane with sodium cyanide to give the title product m.p. 290-291°C dec. Found: C,51.12; H,3.05; N,12.48. $C_{19}H_{13}F_7N_4O$ requires C,51.12; H,2.91; N,12.56%.

EXAMPLE 134

N-[2-(2-Chlorophenyl)-2-hydroxyethyl]-4-(2-methylimidazo[4,5-c]-pyrid-1-yl)benzamide

2-(2-Chlorophenyl)-2-hydroxyethylamine (2.56 mmol, 440 mg) and triethylamine (3.15 mmol, 318 mg) were dissolved in

dichloromethane (20 ml) and the solution cooled in an ice bath. A suspension of 4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)benzoylchloride (1.57 mmol 426 mg) in dichloromethane (20 ml) was added and the mixture stirred at 0°C for 15 minutes then at room temperature for 45 minutes. The mixture was poured into 1N hydrochloric acid and the organic phase separated. The aqueous phase was basified with 2N sodium hydroxide then extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. Purification was effected by column chromatography on silica eluting with dichloromethane/ methanol/ ammonia 94:6:0.1 and the product-containing fractions evaporated to dryness. The resulting oil was dissolved in a little dichloromethane and the product precipitated with cold ether, (0.24 g, 37%). M.p. 126-128°C. Found: C,63.52; H,4.61; N,13.19. $C_{22}H_{19}ClN_4O_2$. 0.5 H_2O requires C,63.54; H,4.81; N,13.47%.

EXAMPLE 135

3RS,4SR-7,8-Dichloro-3-methoxycarbonyl-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one

Sodium metal (846 mg, 36.8 mmol) was dissolved in dry methanol (250 ml) under nitrogen. Dimethyl 2-(2-amino-4,5-dichlorophenyl)-1-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-ethyl-malonate (from Example 117, 16.15 g, 30.16 mmol) was added and the mixture was heated at reflux for 4.5 hours, cooled and poured into 15 ml of 4N hydrochloric acid and ice. The pH was adjusted to 7 by the addition of saturated aqueous sodium bicarbonate and the product was extracted into dichloromethane (4 x 150 ml). The combined extracts were dried ($MgSO_4$) and

concentrated under reduced pressure to give a white solid (14.62 g, 96%). A portion, recrystallised from methanol/dichloromethane had m.p. 221-223°C. The stereochemistry of the product was assigned from the H3-H4 coupling constant (9 Hz). Found: C,60.29; H,4.11; N,11.50. $C_{25}H_{20}Cl_2N_4O_3$ requires C,60.62; H,4.07; N,11.31%.

EXAMPLE 136

7,8-Dichloro-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,-4,5-tetrahydro-1H-1-benzazepin-2-one

A mixture of 7,8-dichloro-3-methoxycarbonyl-4-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (14.42 g, 29.1 mmol) and lithium iodide (19.36 g, 145.5 mmol) in dry pyridine (200 ml) was heated at reflux under nitrogen for 2 hours. The mixture was concentrated under reduced pressure, and purified by flash chromatography (gradient elution with ethyl acetate/methanol) to give the title compound (9.52 g, 75%), m.p. 314-316°C (after recrystallisation from methanol/dichloromethane). Found: C,62.14; H,4.24; N,12.23. $C_{23}H_{18}Cl_2N_4O.0.5\ H_2O$ requires C,61.89; H,4.29; N,12.55%.

EXAMPLE 137

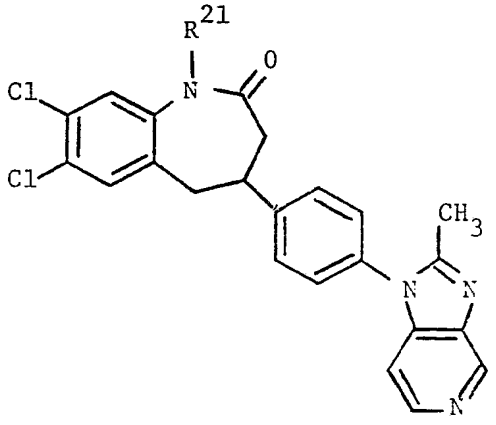
7,8-Dichloro-1-methyl-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-2,3,4,5-tetrahydro-1H-benzazepin-2-one

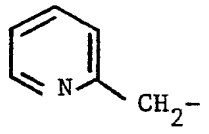
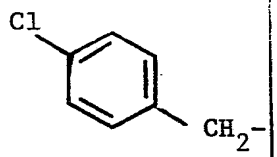
A mixture of 7,8-dichloro-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one (1.093 g, 2.5 mmol) and sodium hydride (150 mg, 60% dispersion in oil, 3.75 mmol), in dry dimethylformamide (10 ml) under nitrogen at room

temperature was sonicated for 5 minutes then stirred for a further 1 hour. Methyl iodide (171 microlitres, 2.75 mmol) was added to the light brown solution and the mixture was stirred for 1.25 hours , then poured into excess ice cold dilute hydrochloric acid. The solution was rendered basic by the addition of saturated aqueous sodium bicarbonate and the product was extracted with dichloromethane (4 x 125 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with ethyl acetate/ methanol (9:1) to give a white solid (848 mg, 75%), m.p. 259-261°C (after recrystallisation from ethyl acetate). Found: C,63.33; H,4.74; N,11.85. $C_{24}H_{20}Cl_2N_4O$. 0.25 $CH_3CO_2C_2H_5$ requires C,63.43; H,4.68; N,11.84%.

EXAMPLES 138-139

The following compounds were prepared from 7,8-dichloro-4-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3,4,5-tetrahydro-1H-1-benzazepin-2-one by the method of Example 137, using 2-picolyl chloride and 4-chlorobenzyl chloride instead of methyl iodide.



Example No	R^{21}	m.p. °C	Analysis% (theoretical in brackets) C	H	N
138		135-137	65.02 (64.81	4.39 4.50	13.19 13.03)+
139		208-210	63.97 (64.12	4.05 4.13	9.86 9.97)

+ Calculated for hemihydrate

EXAMPLE 140

6-[4'-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-5-cyano-2H-1,7-dihydro[3,4]benzazepin-2-one

A solution of hexane-washed sodium hydride in dimethylsulphoxide (4 mg in 0.5 ml) was added to a stirred solution of 2-(2-cyanomethylbenzylamido)-4'-(2-methylimidazo[4,5-c]pyrid-1-yl)acetophenone (0.05 g, 0.12 mmol) in dimethylsulphoxide (1 ml). The solution was stirred at ambient temperature for 16 hours, then partitioned between ethyl acetate and brine. The organic layer was washed with brine, dried ($MgSO_4$) and the solvent evaporated to give a yellow solid (0.028 g). Flash chromatography, eluting with 5 then 15% methanol in ethyl acetate, afforded the title product as a yellow solid (0.011 g, 23%), m.p. above 320°C. ^1H NMR

($CDCl_3$): 2.62(3H,s), 4.58(2H,s), 7.17(1H,d J=5.7Hz) 7.45(2H,d J=8.5Hz), 7.60(2H,m), 7.76(1H, t J=7.5Hz), 8.13(2H,d J=8.5Hz), 8.17(1H,s), 8.43(2H,m) and 9.08(1H,s).

EXAMPLE 141

Ethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-2-(2'-nitrophenylacetyl)-2-benzoylacetate

Hexane-washed sodium hydride (0.053 g, 2.2 mmol) was added to a stirred solution of ethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-benzoylacetate (0.65 g, 2 mmol) in dry tetrahydrofuran (8 ml). After 0.5 hours, solid 2-nitrophenacyl bromide was added in portions and the resultant brown solution was stirred for 1 hour. The mixture was partitioned between ethyl acetate and water, buffering the aqueous phase to pH 7 with 1M hydrochloric acid. The organic layer was dried ($MgSO_4$) and evaporated to dryness. Flash chromatography eluting with 5% methanol in ethyl acetate afforded the title product as a foam (0.61 g, 63%). ^1H NMR ($CDCl_3$): 1.29 (3H,t J=7.5Hz), 2.67(3H,s), 3.68(1H,dd J=16,5Hz), 3.79(1H,dd J=16,8Hz), 4.28(2H,q, J=7.5Hz), 5.23(1H,dd J=8,5Hz), 7.19(1H,d J=5.3Hz), 7.60(2H,d J=8.5Hz), 7.69(2H,m), 7.83(1H, t J=5.5Hz), 8.18(1H, d J=9Hz), 8.40(2H,d J=8.5Hz), 8.50(1H,d J=5.4Hz), 9.12(1H,s).

EXAMPLE 142

1-[4'-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-4-(2'-nitrophenyl)butane-1,4-dione

A solution of ethyl 4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-2-(2'-nitrophenylacetyl)-2-benzoylacetate (0.6 g, 1.23 mmol) in 2M

hydrochloric acid (12 ml) was heated at 100°C for 5 hours then cooled and basified with solid sodium hydrogen carbonate and partitioned between ethyl acetate and water. The aqueous layer was re-extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and the solvent evaporated. Flash chromatography, eluting with 3% methanol in ethyl acetate afforded the title compound as a yellow solid (0.186 g, 37%). ^1H NMR ($CDCl_3$): 2.62(3H,s), 3.37 and 3.62 (each 2H, t J=5.9Hz), 7.15(1H,d J=5.9Hz), 7.55(2H,d 8.4Hz), 7.70(2H,m), 7.80(1H,m), 8.18(1H,d,J=8.2Hz), 8.31(2H,d J=8.4Hz), 8.44(1H,d J=5.5Hz) and 9.10(1H,s).

EXAMPLE 143

1-(2'-Aminophenyl)-4-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]butane-1,4-dione

A solution of 1-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]-4-(2'-nitrophenyl)butane-1,4-dione (0.18 g, 0.43 mmol) in ethanol (8 ml) was hydrogenated over 5% palladium on carbon (0.3 g) at 30 p.s.i. (2.1 bar) and 22°C for 2 hours. The catalyst was filtered off and the filtrate was evaporated to yield a pale-yellow foam (0.166 g, 100%). ^1H NMR ($CDCl_3$): 2.63(3H,s), 3.45 and 3.54 (each 2H,t J=7Hz), 6.25 br (2H,s), 6.70(2H,m), 7.27(2H,m), 7.52(2H,d J=8.5Hz), 7.90(2H,d J=9.5Hz), 8.32(2H,d J=8.5Hz) 8.46(1H,d J=4.5Hz) and 9.08(1H,s).

EXAMPLE 144

7-[4'-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1H-4,5-dihydro-[2,3]-benzazepin-4-one

A solution of 1-(2'-aminophenyl)-4-[4'-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]butane-1,4-dione (0.166 g, 0.43 mmol) in toluene (16 ml) and acetic acid (2 ml) was heated at reflux for 5 hours, then evaporated to dryness. Flash chromatography, eluting with 5% methanol in ethyl acetate afforded a foam which was crystallised from ethyl acetate to give the title 4,5-dihydro[2,3]benzazepin-4-one (0.036 g, 23%), M.p. 223-227°C. ^{1}H NMR ($CDCl_3$): 2.60(3H,s), 3.35(2H,d J=7.5Hz), 5.36(1H,t J=7.5Hz), 6.59br(1H,s), 7.10(3H,m), 7.43(2H,d J=9Hz), 7.53(2H,d J=9Hz), 7.72(2H,d J=8.5Hz), 8.11(1H,d J=8Hz), 8.42(1H,d, J=4.5Hz), 9.10(1H,s).

EXAMPLE 145

3-(2-Carboxyphenyl)-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]propenenitrile

(a) A mixture of 4-aminobenzyl cyanide (29.2 g, 0.22 mmol) and 4-chloro-3-nitropyridine (42.0 g, 0.27 mmol) in ethanol (550 ml) was stirred at room temperature overnight. The solid which had precipitated was dissolved in water (1 litre) and neutralised with saturated aqueous sodium bicarbonate. The product was extracted into dichloromethane (1 x 100 ml and 2 x 500 ml), and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a 4-(4-cyanomethylphenyl)amino-3-nitropyridine (55.5 g, 99%) as a bright yellow solid.

(b) A solution of the nitropyridine (10.0 g, 39.4 mmol) prepared

in (a) above in ethanol:dichloromethane (2:1, 300 ml) was hydrogenated over 10% palladium on carbon (1.0 g) at 20 p.s.i. (1.4 bar) and at room temperature for 2 hours. The catalyst was filtered off and the solvent removed under reduced pressure to give 3-amino-4-(4-cyanomethylphenyl)aminopyridine (8.5 g, 96%), which was used directly for the next reaction.

(c) A mixture of the diaminopyridine (8.5 g, 37.9 mmol) (prepared in (b) above), acetic acid (25 ml) and acetic anhydride (25 ml) was heated at reflux for 16 hours. After being cooled, the excess reagents were removed under reduced pressure and the residue was dissolved in water (150 ml). This solution was rendered basic by the addition of concentrated aqueous ammonia solution and the product was extracted into dichloromethane (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with ethyl acetate/methanol (9:1) to give 1-(cyanomethyl)-4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzene (7.43 g, 79%), as a brown solid.

(d) 1-(Cyanomethyl)-4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzene (272 mg, 1.1 mmol) in dry methanol (1 ml) was treated with a solution of sodium methoxide (250 microlitres, 5.4M in methanol, 1.1 mmol) at room temperature under nitrogen. After the mixture had been stirred for 20 minutes, 2-carboxybenzaldehyde (150 mg, 1.0 mmol) was added, and the mixture was heated at reflux for 2 hours. The mixture was cooled, neutralised with acetic acid, and concentrated under reduced pressure to give the title compound (417 mg) which was used directly for Example 146 without further purification. ^1H NMR (CD_3OD): 2.65(3H,s), 7.38(1H,d,J 5Hz),

7.54(2H,m), 7.69(2H,d,J 8Hz), 7.89(1H,m), 8.02(1H,m), 8.07(2H,d, J 8Hz), 8.39(1H,d,J 5Hz), 8.65(1H,s), 8.94(1H,s).

EXAMPLE 146

4-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-1H-2-benzazepin-1,3-dione

A mixture of 3-(2-carboxyphenyl)-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propenenitrile (410 mg, 1.08 mmol) and polyphosphoric acid (5 ml) was heated at 100°C for 2.5 hours, cooled and treated with ice water (20 ml). The resulting solution was neutralised with dilute aqueous ammonia and the product was extracted into dichloromethane. The extracts were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate/methanol (4:1) followed by recrystallisation from hot ethanol to give the title 2,3-dihydro-1H-2-benzazepin-1,3-dione (49 mg, 12%) m.p. 273-276°C. Found: C,71.64; H,4.34; N,14.37. $C_{23}H_{16}N_4O_2 \cdot 0.25\ H_2O$ requires C,71.76; H,4.32; N,14.56%.

EXAMPLE 147

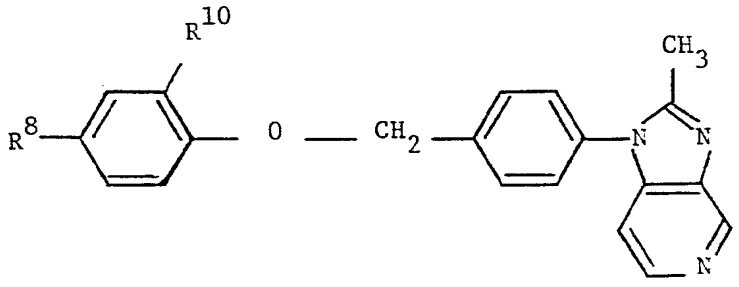
2-Methyl-1-[4-(3-pyridyloxymethyl)phenyl]-imidazo[4,5-c]pyridine fumarate

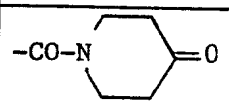
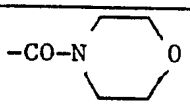
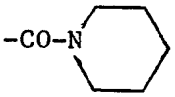
4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol (0.48 g, 2 mmol) was treated with 48% hydrobromic acid (8 ml) as described in Example 101. The crude benzylic bromide was dissolved in dimethylsulphoxide (2 ml) and added to a mixture of 3-hydroxy pyridine (0.38 g, 4 mmol) and flake potassium hydroxide (0.68 g, 12 mmol) in dimethylsulphoxide (8 ml) at room temperature. After

being stirred for 16 hours, the mixture was poured onto ice, neutralised with dilute hydrochloric acid, and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with dichloromethane/methanol). Fractions containing the product were combined, concentrated under reduced pressure, and treated with fumaric acid (60 mg) in methanol. The methanol was removed under reduced pressure, the residue was dissolved in water and freeze-dried, to give a pale yellow powder, (145 mg, 15%), m.p. 84°C. Found: C,61.59; H,4.68; N,11.37. $C_{19}H_{16}N_4O$. 1.5 $C_4H_4O_4$ requires C,61.22; H,4.52; N,11.42%.

EXAMPLES 148-152

Examples 148-151 were prepared by the method of Example 1 using 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol and the appropriate phenol. Example 152 was prepared similarly using the procedure of Example 147 but isolating the product as the free base.



Example No	R^8	R^{10}	m.p. °C	Analysis % (theoretical in brackets) C	H	N
148	H	Br	151-152	60.59 (60.93	4.16 4.09	10.42 10.66)
149	Cl	$-CON(C_2H_5)_2$	59-60	65.22 (65.56 (hemihydrate)	5.66 5.72	11.94 12.23)
150	Cl		119-120	63.34 (63.35 (hydrate)	5.31 5.11	11.26 11.37)
151	Cl		175	64.24 (64.86	5.10 5.01	11.92 12.10)
152	Cl		159-162	67.36 (67.75	5.39 5.47	12.08 12.15)

EXAMPLE 153

1-(2-Hydroxy-5-methylphenyl)-3-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-propen-1-one

A mixture of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde

(Preparation 13) (3.555 g, 15 mmol), 2-hydroxy-5-methyl-acetophenone (2.225 g, 15 mmol) and lithium hydroxide hydrate (3.720 g, 75 mmol) in ethanol/water (96:4) (100 ml) was stirred under nitrogen at room temperature for 18 hours. The red suspension was concentrated under reduced pressure, and the residue was dissolved in excess dilute hydrochloric acid. The solution was poured into a mixture of excess saturated aqueous sodium bicarbonate and dichloromethane (100 ml). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 200 ml). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallised from ethyl acetate/dichloromethane to give orange prisms (2.425 g, 44%), m.p. 229-230°C. Found: C,73.99; H,5.28; N,11.30. $C_{23}H_{19}N_3O_2$. 0.25 H_2O requires C,73.88; H,5.26; N,11.24%.

EXAMPLE 154

1-(5-Fluoro-2-hydroxyphenyl)-3-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-propen-1-one

The title compound was prepared by the method of Example 153, using the appropriate 2-hydroxyacetophenone and 4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)benzaldehyde. The product was obtained as a bright orange solid. ^1H NMR (300 MHz, $CDCl_3$): 2.60(3H,s), 7.02(1H,m), 7.13(1H,d,J 4Hz), 7.30(1H,m), 7.48(2H,d,J 8Hz), 7.61(1H,m), 7.64(1H,d,J 18Hz), 7.92(2H,d,J 6Hz), 8.00(1H,d,J 18Hz), 8.41(1H,d,J 4Hz), 9.08(1H,s), 12.42(1H,s).

EXAMPLE 155

1-(4,5-Dimethyl-2-hydroxyphenyl)-3-[4-(2-methylimidazo[4,5-c]-pyrid-1-yl)phenyl]-2-propen-1-one

The title compound was prepared by the method of Example 153, and was obtained as a bright yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) 2.28(3H,s), 2.31(3H,s), 2.60(3H,s), 6.86(1H,s), 7.13(1H,d,J 5Hz), 7.45(2H,d,J 8Hz), 7.64(1H,s), 7.73(1H,d,J 14Hz), 7.91(2H,d,J 8Hz), 7.97(1H,d,J 14Hz), 8.41(1H,d,J 5Hz), 9.07(1H,s), 12.58(1H,s).

EXAMPLE 156

2RS-6-Methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-4H-benzo[b]pyran-4-one

A mixture of 1-(2-hydroxy-5-methylphenyl)-3-[4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]-2-propen-1-one (400 mg, 1.08 mmol) and anhydrous potassium fluoride (50% on Celite, 200 mg) in dry methanol (20 ml) was heated under reflux for 48 hours, then cooled and filtered. The filtrate was concentrated under reduced pressure, and purified by flash chromatography on silica gel, eluting with dichloromethane/isopropanol (20-10:1). Fractions containing the product were combined, concentrated and recrystallised twice from ethanol to give a creamy-coloured solid (42 mg, 11%), m.p. 202-203°C. Found: C,73.72; H,5.10; N,11.08. $C_{23}H_{19}N_3O_2 \cdot 0.33\ H_2O$ requires C,73.59; H,5.29; N,11.19%.

EXAMPLE 157

2RS,4RS-4-Hydroxy-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-4H-benzo[b]pyran

The product from Example 153 (2.43 g, 6.54 mmol) was dissolved in a mixture of methanol (60 ml), water (40 ml) and aqueous sodium hydroxide (1M, 3.27 ml, 3.27 mmol) at room temperature with stirring, and then sodium borohydride (254 mg, 6.54 mmol) was added. The mixture was stirred for 18 hours at room temperature, and then partitioned between dichloromethane (3 x 50 ml) and 0.1M aqueous sodium hydroxide (200 ml). The organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate:methanol:diethylamine (90:5:5) to give a white solid (1.57 g, 65%), m.p. 238-241°C (after trituration with methanol/ethyl acetate). Found: C,73.73; H,5.62; N,11.38. $C_{23}H_{21}N_3O_2 \cdot 0.2\ H_2O$ requires C,73.66; H,5.75; N,11.20%.

The stereochemistry of the product was assigned from the coupling constants in the ^1H NMR spectrum (300 MHz, $CDCl_3$) as follows: H-2 (dd, J 1 and 11.6Hz) and H-4 (dd, J 6 and 10.5Hz), hence both hydrogens are axial.

EXAMPLE 158

2RS,4RS-6-Fluoro-4-hydroxy-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-4H-benzo[b]pyran

The product of example 154 was cyclised following the method

of Example 157 to give the title compound, m.p. 219-220°C (from methanol). Found: C,70.50; H,4.73; N,11.21. $C_{22}H_{18}FN_3O_2$ requires C,70.38; H,4.83; N,11.19%.

EXAMPLE 159

2RS, 4RS-6,7-Dimethyl-4-hydroxy-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-4H-benzo[b]pyran

The product of Example 155 was cyclised following the method of Example 157 to give the title compound, m.p. 243-246°C (from methanol/dichloromethane). Found: C,74.94; H,6.05; N,10.90. $C_{24}H_{23}N_3O_3$ requires C,74.78; H,6.01; N,10.90%.

EXAMPLE 160

2RS,4RS-4-Methoxy-6-methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2,3-dihydro-4H-benzo[b]pyran

The compound from Example 157 (371 mg, 1.0 mmol) was dissolved in dry dimethylformamide (8 ml) and sodium hydride (48 mg, 60% dispersion, 1.2 mmol) was added at room temperature. After 45 minutes methyl iodide (68 µl, 1.1 mmol) was added and the mixture was stirred for a further 1 hour. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate (20 ml), washed with water (10 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with dichloromethane:methanol (16:1), followed by recrystallisation from diethyl ether to give a white solid (200 mg, 52%), m.p. 151-153°C. Found: C,74.74; H,6.03; N,10.91. $C_{24}H_{23}N_3O_2$ requires C,74.78; H,6.01; N,10.90%.

EXAMPLE 161

2RS,4RS-4-(4-Fluorophenyl)-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]-1,3-dioxane

The method of Example 37 was followed using 4-fluoro-(1,3-dihydroxypropyl)benzene to give the title compound, m.p. 70°C. Found: C,69.48; H,5.29; N,9.99. $C_{23}H_{20}FN_3O_2$. 0.5 H_2O requires C,69.33; H,5.31; N,10.55%.

EXAMPLE 162

2-Methyl-1-[4-(phenylmethyl)phenyl]-imidazo[4,5-c]pyridine

a) A mixture of 4-chloroimidazo[4,5-c]pyridine (670 mg, 4.0 mmol), p-fluorobenzophenone (880 mg, 4.4 mmol) and anhydrous potassium carbonate (607 mg, 4.4 mmol) in dry dimethylformamide (8 ml) was stirred at reflux for 3 hours. The mixture was then concentrated under reduced pressure, dissolved in dichloromethane (75 ml) and washed with water. The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with ethyl acetate/dichloromethane (3:2) to give 1-(4-benzoyl)phenyl-2-methyl-imidazo[4,5-c]pyridine, (1.14 g, 82%), m.p. 205-207°C (from ethyl acetate).

b) The compound from (a) above (612 mg, 1.94 mmol) was hydrogenated over 30% palladium on carbon (500 mg) in a mixture of ethanol (60 ml) and dichloromethane (15 ml) in the presence of magnesium oxide (612 mg) at 60 p.s.i. (4.1 bar) and 40°C for 2 hours. The mixture was cooled, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica eluting with dichloromethane/methanol

(16:1) to give 2-methyl-1-[4-(hydroxy(phenyl)methyl)phenyl]-imidazo[4,5-c]pyridine (430 mg, 77%), m.p. 232-234°C (from methanol).

(c) The product from step (b) above, (240 mg, 0.76 mmol) was added to a mixture of trifluoroacetic acid (8 ml) and triethylsilane (145 µl, 0.91 mmol), and the mixture was stirred at 50°C for 1 hour. The mixture was concentrated under reduced pressure, and the residue was dissolved in dichloromethane (20 ml) and rendered basic by the addition of saturated aqueous sodium bicarbonate. The aqueous layer was separated, extracted with dichloromethane (2 x 15 ml), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica, eluting with ethyl acetate/methanol (6:1) to give the title compound (205 mg, 90%), which was further purified by reverse-phase h.p.l.c. (C_{18} silanized silica, eluting with methanol/water, 85:15) to give a white solid, m.p. 131-132°C (from aqueous methanol). Found: C,80.79; H,5.75; N,13.70. $C_{20}H_{17}N_3$ requires C,80.24; H,5.72; N,14.04%.

PREPARATION 1

Ethyl [4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]acetate

a) Ethyl 4-aminophenylacetate (17.7 g, 0.1 mole) and sodium bicarbonate (8.4 g, 0.1 mole) were stirred in ethanol (200 ml). 4-Chloro-3-nitropyridine (15.9 g, 0.1 mole) was added as a solution in ethanol (50 ml) and the whole stirred at room temperature for 3 hours. The mixture was then evaporated to low bulk and poured into ethyl acetate (500 ml) and washed with water (200 ml). The organic phase was then extracted with 0.5N hydrochloric acid and the combined aqueous extracts basified with 2N sodium hydroxide and extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was recrystallised from aqueous ethanol to give ethyl 4-(3-nitro-pyrid-4-ylamino)phenyl acetate (7.32 g), m.p. 124-126°C. A further 8.56 g was recovered from the mother liquors.

b) The above product (15.7 g) was hydrogenated at 60 p.s.i. (4.1 bar) over 5% palladium on charcoal for 3 hours at room temperature. Filtration and evaporation of the solvent gave ethyl 4-(3-amino-pyrid-4-ylamino)phenyl acetate (14.1 g).

c) Ethyl 4-(3-amino-pyrid-4-ylamino)phenyl acetate (14.1 g, 52 mmol), glacial acetic acid (100 ml) and acetic anhydride (100 ml) were mixed and heated at reflux under nitrogen for 1½ hours. The cooled solution was evaporated to dryness and basified with 10% aqueous sodium carbonate solution then extracted with dichloromethane (3 x 100 ml). The combined organic extracts were evaporated to dryness and purified by chromatography on silica eluting with dichloromethane/ethanol to give ethyl [4-(2-methyl-

imidazo[4,5-c]pyrid-1-yl)phenyl]acetate (13.6 g).

PREPARATION 2

Ethyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propanoate

Ethyl [4-(2-methyl-imidazo[4,5-c]pyrid-1-yl)phenyl]acetate (7.4 g, 25 mmol) was dissolved in tetrahydrofuran (100 ml) and the solution cooled to -70°C. Lithium diisopropylamide (1.5M, 18.4 ml, 27.5 mmol) was added under nitrogen and the resulting suspension stirred for 15 minutes. Methyl iodide (3.91 g, 27.5 mmol) was added and the mixture allowed to come to room temperature over 2½ hours. The reaction was then quenched with hydrochloric acid (25 ml, 1N) and evaporated to low bulk, the solution was basified with sodium carbonate solution and extracted with dichloromethane (3 x 100 ml). The organic extracts were dried, filtered and evaporated to dryness. The residue was purified by column chromatography on silica to yield ethyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]propanoate (4.5 g, 58%), m.p. 78-80°C.

PREPARATION 3

2-Methyl-2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propanol

Ethyl 2-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)-phenyl]propanoate (2.94 g, 9.5 mmol) was dissolved in tetrahydrofuran (50 ml) and cooled in an ice bath under nitrogen. Lithium aluminium hydride (0.19 g, 5 mmol) was added portionwise over 2 minutes. The mixture was stirred at 0°C for 10 minutes then at room temperature for 3 hours. Further lithium aluminium hydride (0.19 g) was added and after 15 minutes water was added cautiously. The mixture was acidified with N hydrochloric acid (15

ml) then basified with sodium carbonate solution and extracted with dichloromethane (2 x 100 ml). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The residue was purified by column chromatography on silica eluting with 10% methanol in dichloromethane to give the title product (2.3 g). Found: C,71.78; H,6.45; N,15.56. $C_{16}H_{17}N_3O$ requires C,71.91; H,6.37; N,15.73%.

PREPARATION 4

1-Phenyl-1,3-propanediol

A solution of ethyl 3-phenyl-3-hydroxy-propanoate (4.7 g, 26 mmol) in anhydrous ether (20 ml) was added dropwise to a cold (0°C), stirred suspension of lithium aluminium hydride in diethyl ether (50 ml). A vigourous reaction ensued during the addition. The resultant mixture was stirred at 18°C for 15 hours, then cautiously treated with water (1.1 ml), 15% aqueous sodium hydroxide (1.1 ml) and water (3.1 ml). The mixture was filtered through a filter pad and evaporated to a pale-yellow oil. Silica-gel chromatography afforded the title diol as a colourless, viscous oil (3.27g, 91%).

PREPARATION 5

2-Phenyl-1,3-propanediol

A solution of tropic acid (3 g, 18 mmol) in tetrahydrofuran (20 ml) was added dropwise to a cold (0°C), stirred suspension of lithium aluminium hydride in tetrahydrofuran (40 ml). After 2 hours, the mixture was cautiously hydrolysed by addition of water (0.8 ml), 15% aqueous sodium hydroxide (0.8 ml) and water (2.5 ml). The mixture was filtered through a filter pad and evaporated

to a pale-yellow oil. Chromatography on silica eluting with diethyl ether afforded the title diol as a colourless oil which crystallised on standing. M.p. 41-46°C.

PREPARATION 6

1,2-Bis(trimethylsilyloxy)-1-phenylethane

Butyllithium (1.6M in hexane; 19 ml, 30 mmol) was added dropwise to a cold (-20°C), stirred solution of phenylethanediol (2 g, 14.5 mmol) in tetrahydrofuran (80 ml). After 10 minutes, neat chlorotrimethyl-silane (4.5 ml, 35 mmol) was added. After 30 minutes, all volatiles were removed under vacuum and the residue was partitioned between hexane and saturated sodium bicarbonate solution. The hexane layer was dried over magnesium sulphate and evaporated to give the title product as a pale-yellow oil (4g, 97%).

PREPARATION 7

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]-2-methyl-oxirane

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)acetophenone (430 mg 1.7 mmol) was dissolved in tetrahydrofuran and cooled in an ice bath under nitrogen. Dimethylsulphoxonium methylide (0.6M in tetrahydrofuran, 5 ml, 3 mmol) was added and the solution stirred at room temperature for 4 days. The solvent was removed under vacuum and the residue purified by column chromatography on silica eluting with dichloromethane/methanol (97:3). The title compound crystallised on removal of the solvent under vacuum (416 mp, 92%). ^{1}H NMR $CDCl_3$: 9.08(1H,s), 8.40(1H,d J=6Hz), 7.57(2H,d,J=9Hz), 7.38(2H,d,J=9Hz), 7.10(1H,s), 4.02(1H,t), 3.28(1H,m),

2.90(1H,m), 2.63(3H,s).

PREPARATION 8

2-[4-(2-Methylimidazo[4,5-c]pyrid-1-yl)phenyl]oxirane

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde (1.19 g, 5mmol) was dissolved in tetrahydrofuran (20 ml) and the solution cooled in an ice bath. Dimethyl-sulphoxonium methylide (0.6M in tetrahydrofuran; 15ml, 9 mmol) was added and the resulting white suspension stirred at 0°C for 1 hour then at room temperature for 1 hour. The mixture as evaporated to 5 ml, poured into brine and extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was further purified by column chromatography on silica eluting with dichloromethane/methanol (97:3) to give the title oxirane as a clear, unstable oil which turned red on standing (362 mg, 29%).

PREPARATION 9

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)acetophenone

(a) 4-(4-Acetylphenyl)amino-3-nitropyridine hydrochloride

A solution of 4-chloro-3-nitropyridine hydrochloride (9.75 g, 50 mmol) in ethanol (40 ml) was added to a slurry of p-aminoacetophenone (6.76 g, 50 mmol) in ethanol (25 ml), and the mixture was stirred at room temperature overnight. The mixture was chilled in ice, and the yellow solid filtered off and dried (10.1 g, 69%). m.p. 197-200°C.

b) 4-(4-acetylphenyl)amino-3-aminopyridine

4-(4-Acetylphenyl)amino-3-nitropyridine hydrochloride (2.0 g,

78.8 mmol) was partitioned between aqueous sodium hydroxide and dichloromethane (3 x 20 ml). The combined organic phases were washed with water (20 ml) and concentrated under reduced pressure to give a solid. Ethanol (20 ml) was added, and the solution was hydrogenated over 5% palladium on carbon (0.2 g) at 50 p.s.i. (3.4 bar) for 3.5 hours. The catalyst was filtered off, and the solvent removed under reduced pressure to give a brown solid, (1.8 g, ca 100%) which was used directly for the next stage without purification.

(c) 4-2(-Methylimidazo[4,5-c]pyrid-1-yl)acetophenone

A solution of 4-(4-acetylphenyl)amino-3-aminopyridine (68.0 g, 0.3 mmol) in acetic acid (204 ml) and acetic anhydride (204 ml) was heated at 95°C for 1.5 hours then cooled and concentrated under reduced pressure. The residue was dissolved in water (500 ml) and rendered basic by the addition of saturated aqueous ammonia. The product was filtered off, washed with water (2 x 100 ml) and dried under vacuum to give the title compound, (61.0 g, 81%) as a brown solid, m.p. 155-156°C (from water).

PREPARATION 10

Ethyl 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzoylacetate

A solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl-acetophenone(17.5 g, 69.7 mmol) in dry tetrahydrofuran (175 ml) was added to a slurry of sodium hydride (3.68 g, 153 mmol) in a mixture of dry tetrahydrofuran (35 ml) and diethyl carbonate (24.7 g, 209 mmol) at reflux with stirring over 45 minutes. After a further 1 hour, the mixture was cooled, hexane (200 ml) was added, and the resulting precipitate was filtered off and washed with

hexane (2 x 100 ml). The solid was suspended in ethyl acetate (200 ml) and acetic acid (10.2 g) was added. After stirring for 15 minutes, water (200 ml) was added, and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (100 ml) and the combined organic solutions were washed with water (200 ml), dried ($MgSO_4$) and concentrated to give the title product as a gum (17.3 g, 77%). Further purification by flash chromatography (eluting with ethyl acetate/methanol (7:1) gave the title compound as a white solid. m.p. 165-166°C.

PREPARATION 11

3-Hydroxy-3-[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl)propanol

Sodium borohydride (0.38 g, 10 mmol) was added to a stirred suspension of ethyl 4-(2-methylimidazo[4,5-c]pyrid-1-yl]-benzoyl acetate (2.4 g, 7.4 mmol) in isopropanol (20 ml) and the mixture stirred at ambient temperature for one week. The solution was concentrated and partitioned between water and dichloromethane. The organic layer was dried over magnesium sulphate and evaporated to an oil. Chromatography on silica eluting with methanol in ethyl acetate afforded a colourless foam which crystallised from dichloromethane (0.25 g, 12%). M.p. 148-50°C. Found: C,66.80; H,6.04; N,14.57. $C_{16}H_{17}N_3O_2.0.25\ H_2O$ requires C,66.76; H,6.13; N,14.60%.

PREPARATION 12

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzonitrile

a) 4-Cyanoaniline (6.894 g, 58.4 mmol) was added to a solution of 4-chloro-3-nitropyridine (9.26 g, 58.4 mmol) in ethanol (200

ml) and the mixture was stirred at room temperature for 18 hours. The resulting yellow suspension was poured into 500 ml of ice-cold dilute ammonia and filtered. The solid was treated with 150 ml of boiling ethanol, cooled in ice, and filtered to give N-(4-cyanophenyl)-4-amino-3-nitropyridine, 12.15 g, as a bright yellow powder, m.p. 210-211°C.

b) According to a modification of the method of Pharm. Helv. Acta, 1975, 50, 188., tin dichloride dihydrate (56.4 g, 250 mmol) was added to a suspension of N-(4-cyanophenyl)-4-amino-3-nitropyridine (12.0 g, 50 mmol) in 2N aqueous hydrochloric acid (35 ml), water (150 ml) and ethanol (75 ml) and the resulting mixture was heated to reflux for 10 minutes under nitrogen. The mixture was cooled in ice, poured into ice-cold 2N aqueous sodium hydroxide (400 ml) and filtered. The creamy coloured solid was washed with 2N aqueous sodium hydroxide and water, and then dried in a vacuum desiccator. The product, 3-amino-4-(4'-cyanophenyl)-aminopyridine, 9.31 g, gradually turned reddish brown on exposure to light and air.

c) A mixture of 3-amino-4-(4'-cyanophenyl)aminopyridine (9.31 g, 44.3 mmol), triethyl-orthoacetate (40 ml) and acetic anhydride (30 ml) was heated at reflux for 2 hours under nitrogen, cooled, then concentrated under reduced pressure. The brown residue was dissolved in 1M hydrochloric acid and washed with ethyl acetate (200 ml). The aqueous layer was rendered basic with saturated aqueous ammonia and extracted with dichloromethane (3 x 200 ml). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated to give the title product as a brown solid (6.5 g). ^1H NMR ($CDCl_3$): 2.61(3H,s), 7.13(1H,d, J 6Hz), 7.58(2H,d,J 9Hz),

7.98(2H,d,J 9Hz), 8.45(1H,d,J 6hz), 9.11(1H,s).

PREPARATION 13

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzaldehyde

Nickel-aluminium alloy (1 g) was added to a stirred solution of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (1 g, 4.3 mmol) in 90% formic acid (13 ml) and water (3 ml). The mixture was heated to 120°C when an exothermic reaction initiated, then heated under reflux for an additional 1 hour. The solution was cooled and filtered using a filter aid, washing the filter cake with methanol. The filtrate was concentrated and partitioned between ethyl acetate (100 ml) and saturated aqueous sodium bicarbonate (100 ml). The organic layer was separated, dried over magnesium sulphate and evaporated to dryness. Trituration with ethyl acetate, followed by recrystallisation from isopropanol afforded the aldehyde as a colourless solid (0.2 g, 20%), m.p. 158-160°C. Found: C,70.31; H,4.63; N,17.38. $C_{14}H_{11}N_3O$ requires C,70.87; H,4.67; N,17.71%.

PREPARATION 14

Methyl[4-(2-methylimidazo[4,5-c]pyrid-1-yl)phenyl]propanoate

The procedure described under Preparation 9 was followed but using p-aminophenylpropanoate in place of p-aminoacetophenone to give the title compound (65%) m.p. 88-91°C. Found: C,67.16; H,5.84; N,13.55. $C_{17}H_{17}N_3O_2$. 0.5 H_2O requires C,67.11; H,5.92; N,13.82%.

PREPARATION 15

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzyl alcohol

The procedure described under Preparation 9 was followed but using 4-aminobenzyl alcohol instead of 4-aminoacetophenone to give the title product (83%) m.p. 154-156°C. Found: C,70.10; H,5.22; N,17.89. $C_{14}H_{13}N_3O$ requires C,70.29; H,5.44; N,17.57%.

PREPARATION 16

1-[4-(2-Hydroxyethylphenyl)]-2-methylimidazo[4,5-c]pyridine

The procedure described under Preparation 9 was followed but using 4-aminophenethyl alcohol instead of 4-aminoacetophenone to give the title product (67%) m.p. 196-198°C. Found: C,70.99; H,6.16; N,16.50. $C_{15}H_{15}N_3O$ requires C,71.15; N,5.93; N,16.60%.

PREPARATION 17

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzoic acid

A mixture of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzonitrile (12.0 g, 51.3 mmol) and sodium hydroxide (22.0 g, 0.55 mmol) in a mixture of ethanol (55 ml) and water (55 ml) was heated under nitrogen at reflux for 1½ hours, cooled and concentrated under reduced pressure. The brown residue was dissolved in iced water and glacial acetic acid (33 ml) was added, at which point a buff-coloured solid precipitated. The solid was washed with water and dried under vacuum at 70°C to give the title compound, (9.139 g, 70%). ^{1}H NMR (DMSO-d_6), 2.50(3H,s), 7.25(1H,d,J=5Hz), 7.72(2H,d,J=8Hz), 8.16(2H,d,J=8Hz), 8.30(1H,d,J=5Hz), 8.92(1H,s).

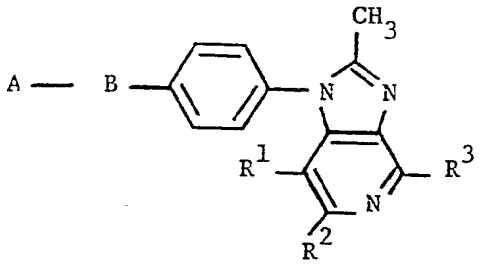
PREPARATION 18

4-(2-Methylimidazo[4,5-c]pyrid-1-yl)benzamide

A mixture of 4-(2-methylimidazo[4,5-c]pyrid-1-yl)benzontrile (4.69 g, 20 mmol) and concentrated sulphuric acid (50 ml) was heated at 110°C with stirring for one hour, then slowly poured onto crushed ice (200 g). The pH of the mixture was adjusted to 8 by addition of aqueous sodium hydroxide and the solution extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and evaporated to a yellow solid (5 g) which was recrystallised from isopropanol to give the title product (2.19 g, 44%), m.p. 194-195°C. Found: C,65.46; H,6.35; N,18.40. $C_{14}N_{12}N_4O.(CH_3)_2CHOH$ requires C,65.36; H,6.45; N,17.94%.

CLAIMS

1. A compound having the general formula:



....(I)

or a pharmaceutically acceptable salt thereof,

wherein A is a C_1-C_8 alkyl, perfluoro(C_1-C_8)alkyl, C_3-C_8 cycloalkyl, aryl or heterocyclic group, wherein said aryl or heterocyclic group may be unsubstituted or substituted with from one to three substituents each independently chosen from C_1-C_4 alkyl, halo, oxo, CO_2R^4, $CONR^5R^6$, OH, C_1-C_4 alkoxy, NH_2, NO_2, CN and $(CH_3)_3SiCH_2$;

B is a C_1-C_5 alkylene or C_2-C_5 alkenylene chain which may optionally be substituted by one or more C_1-C_4 alkyl, C_1-C_4 alkoxy, perfluoro(C_1-C_4)alkyl, C_3-C_7 cycloalkyl, phenyl, oxo, OH, CN, $CONR^5R^6$ or CO_2R^4 groups and wherein up to two carbon atoms in said chain can independently be replaced by O, $S(O)_m$, -N= or NR^7, and wherein said chain or part of said chain, may form, or may form part of, a 5-7 membered saturated or mono-unsaturated ring which may contain a nitrogen atom or NR^7 group, a nitrogen and oxygen atom, or one or two oxygen atoms, said ring being

optionally substituted with any of the foregoing chain substituents, and, in the case where the group A is an aryl or heterocyclic group, the ring may optionally be fused to said aryl or heterocyclic group;

each of R^1, R^2 and R^3 is independently H or CH_3;

R^4 is H, C_1-C_4 alkyl or aryl(C_1-C_4)alkyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or R^5 is H and R^6 is C_3-C_8 cycloalkyl or aryl, or the two groups R^5 and R^6 together with the nitrogen atom to which they are attached, form a piperidino, 4-ketopiperidino,morpholino or piperazinyl group;

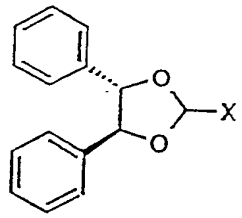
R^7 is H, C_1-C_4 alkyl, CO_2(C_1-C_4)alkyl, aryl(C_1-C_4)alkyl or heteroaryl(C_1-C_4)alkyl;

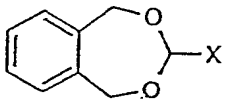
and m is 0, 1 or 2;

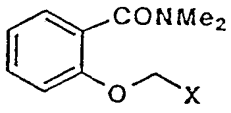
with the proviso that A-B is not $C_2H_5OCOCH_2CO$- or $CH_3COCH_2CO_2CH_2$-.

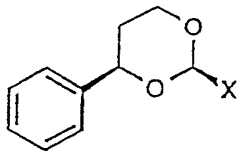
2. A compound according to claim 1 wherein the linking group B, is an ether group having an oxygen atom and up to four carbon atoms in the chain linking the group A to the phenyl ring, and wherein said linking group may optionally have a further oxygen atom in the chain and said chain may optionally be substituted by hydroxy, oxo, C_1-C_4 alkoxy, C_1-C_4 alkyl or phenyl, or wherein the linking group may also form part of a 5 to 7 membered cyclic ether group containing one or two oxygen atoms in the ring which may optionally be substituted by C_1-C_4 alkyl hydroxy, oxo, or C_1-C_4 alkoxy and which may optionally be fused to a phenyl or tetrahydronaphthalene ring.

3. A compound as claimed in claim 2 having the formula:

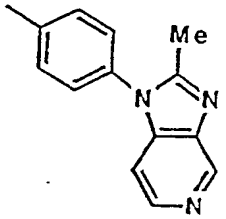






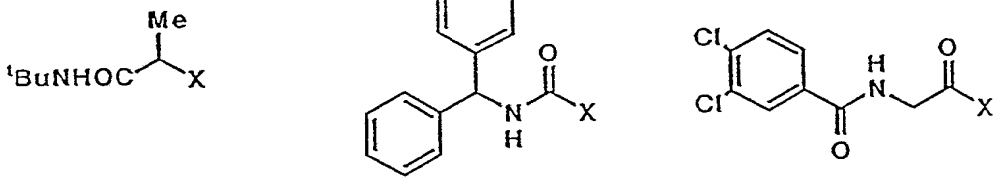


wherein X is:



4. A compound according to claim 1 wherein the linking group B contains an amide group together with up to three further carbon atoms in the chain linking A to the phenyl ring. The nitrogen atom may optionally be substituted by C_1-C_4 alkyl and the chain may optionally be substituted by C_1-C_4 alkyl or phenyl, or include a further oxo substituent.

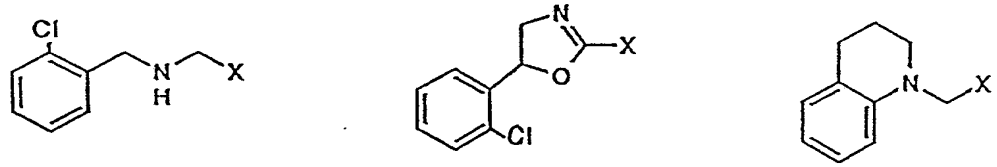
5. A compound as claimed in claim 4 having the formula:



wherein X is as previously defined in claim 3.

6. A compound according to claim 1 wherein the linking group B contains NR^7 or -N=, together with up to four carbon atoms in the chain linking A to the phenyl group, which may optionally be substituted by oxo or $CO_2(C_1-C_4)$-alkyl, wherein R^7 is H, C_1-C_4 alkyl, $CO_2(C_1-C_4)$alkyl or aryl(C_1-C_4)alkyl; and wherein said linking group may optionally be cyclised to form a pyrrolidinyl group or piperidino group, which may optionally be fused to a benzene ring, or it may be an oxazoline ring.

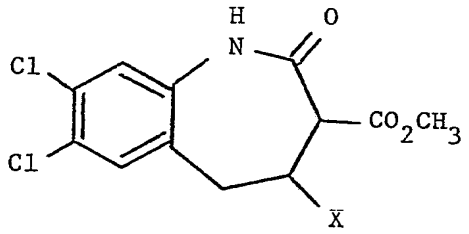
7. A compound as claimed in claim 6 having the formula:

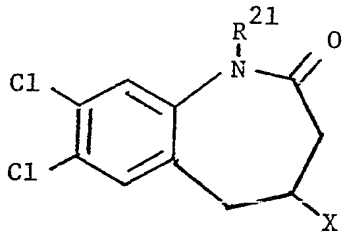


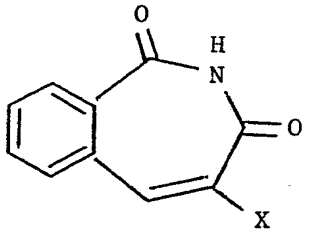
wherein X is as previously defined in claim 3.

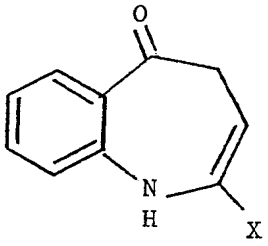
8. A compound according to claim 1 wherein the linking group B is a 7-membered saturated or mono-unsaturated ring containing $-NR^7-$ wherein R^7 is as previously defined in claim 6, and wherein said ring may optionally be substituted with oxo or CO_2CH_3.

9. A compound as claimed in claim 8 having the formula:





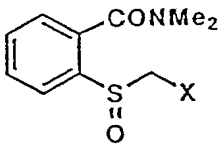


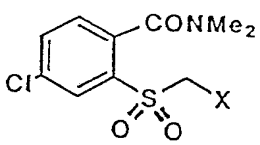


wherein R^{21} is H, methyl, 4-chlorobenzyl or 2-pyridylmethyl and X is as previously defined in claim 3.

10. A compound according to claim 1 wherein the linking group B contains a $S(O)_m$ group together with up to four carbon atoms in the chain linking A to the phenyl ring, where m is 0-2, and wherein the chain may optionally be substituted by C_1-C_4 alkyl or hydroxy.

11. A compound as claimed in claim 10 having the formula:

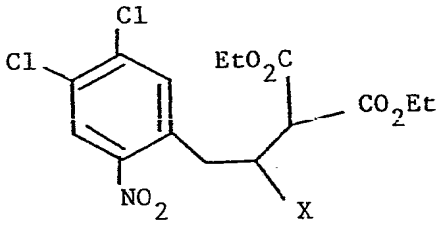


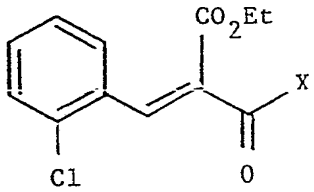


wherein X is as previously defined in claim 3.

12. A compound according to claim 1 wherein the linking group B is a C_1-C_4 alkylene or C_2-C_4 alkenylene group which may optionally be substituted by one or more OH, oxo, CO_2R^4 or perfluoroalkyl groups, wherein R^4 is as previously defined in claim 1.

13. A compound as claimed in claim 12 having the formula:





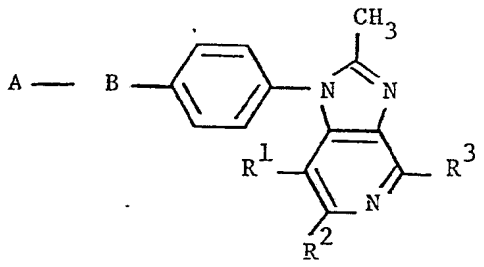
wherein X is as previously defined in claim 3.

14. A pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13, together with a pharmaceutically acceptable diluent or carrier.

15. A compound of the formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 13 for use in medicine, in particular for use in the treatment of allergic, inflammatory and hypersecretory conditions in humans.

PROCESS CLAIMS

16. A process for preparing a compound having the formula:



....(I)

and pharmaceutically acceptable salts thereof,

wherein A is a C_1-C_8 alkyl, perfluoro(C_1-C_8)alkyl, C_3-C_8 cycloalkyl, aryl or heterocyclic group, wherein said aryl or heterocyclic group may be unsubstituted or substituted with from one to three substituents each independently chosen from C_1-C_4 alkyl, halo, oxo, CO_2R^4, $CONR^5R^6$, OH, C_1-C_4 alkoxy, NH_2, NO_2, CN and $(CH_3)_3SiCH_2$;

B is a C_1-C_5 alkylene or C_2-C_5 alkenylene chain which may optionally be substituted by one or more C_1-C_4 alkyl, C_1-C_4 alkoxy, perfluoro(C_1-C_4)alkyl, C_3-C_7 cycloalkyl, phenyl, oxo, OH, CN, $CONR^5R^6$ or CO_2R^4 groups and wherein up to two carbon atoms in said chain can independently be replaced by O, $S(O)_m$, -N= or NR^7, and wherein said chain or part of said chain, may form, or may form part of, a 5-7 membered saturated or mono-unsaturated ring which may contain a nitrogen atom or NR^7 group, a nitrogen and

oxygen atom, or one or two oxygen atoms, said ring being optionally substituted with any of the foregoing chain substituents, and, in the case where the group A is an aryl or heterocyclic group, the ring may optionally be fused to said aryl or heterocyclic group;

each of R^1, R^2 and R^3 is independently H or CH_3;

R^4 is H, C_1-C_4 alkyl or aryl(C_1-C_4)alkyl;

R^5 and R^6 are each independently H or C_1-C_4 alkyl, or R^5 is H and R^6 is C_3-C_8 cycloalkyl or aryl, or the two groups R^5 and R^6 together with the nitrogen atom to which they are attached, form a piperidino, 4-ketopiperidino, morpholino or piperazinyl group;

R^7 is H, C_1-C_4 alkyl, CO_2(C_1-C_4)alkyl, aryl(C_1-C_4)alkyl or heteroaryl(C_1-C_4)alkyl;

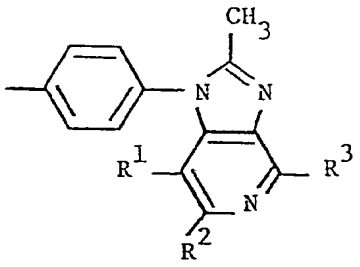
and m is 0, 1 or 2;

which process comprises one of the following-:

a) for compounds of the formula (I) wherein A is Ar and Ar is an aryl or heteroaryl group which may optionally be subsituted as defined in A above and the linking group B is an ether group having an oxygen atom and up to four carbon atoms in the chain linking A to the phenyl ring, said compounds having the formula:

Ar-O-D-X

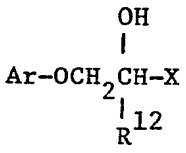
wherein D is a C_1-C_4 alkylene group which may optionally be substituted as defined in B above and X is:



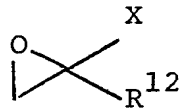
wherein R^1, R^2 and R^3 are as previously defined;

by reaction of a compound of the formula Ar-OH either with a hydroxyalkyl derivative of formula HO-D-X in the presence of triphenyl phosphine and diethylazodicarboxylate or with a halo alkyl derivative of formula hal-D-X, wherein hal is chloro or bromo, in the presence of an acid acceptor, wherein Ar, D and X are as previously defined; and optionally using a chemical transformation reaction to obtain compounds wherein Ar is substituted by $-CO_2R^4$ and R^4 is H or wherein the substituent is $CONR^5R^6$ and R^5 and R^6 are as defined above, or is NH_2; or

b) for compounds of the formula:

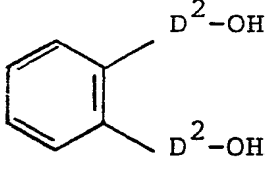


wherein Ar is an aryl group which may optionally be substituted as defined in A above and R^{12} is H or CH_3; by reacting an oxirane of formula



wherein X and R^{12} are as previously defined above, with a phenolic anion of formula $Ar-O^{\ominus}$; or

c) for compounds of the formula (I) wherein B forms a 5-7 membered cyclic diether group, by reaction of an aldehyde of formula HCO-X wherein X is as previously defined in a) above, either with a diol of formula



wherein each D^2 is independently a direct bond or C_1-C_2 alkylene group with the proviso that the total number of carbon atoms in both together does not exceed 2, to give compounds wherein A is a phenyl group benzofused to said cyclic diether group; or by reaction of the aldehyde with a diol of formula A-B^1-OH, wherein A is as previously defined and B^1 is a C_2-C_4 alkylene group optionally substituted by phenyl or with a further oxygen atom in the chain and containing a further OH group separated by from 2 to 4 carbon atoms from the terminal OH group; or by reaction of an aryl aldehyde of formula:

Ar-CHO

wherein Ar is as previously defined in b) above with a diol of formula:

HO-B^1-X

wherein B^1 and X are as previously defined; or

d) for compounds of formula (I) wherein B contain a -O-CO- (ester) group and up to three further carbon atoms in the chain linking A to the phenyl group, either by reaction of an acid of formula HO_2C-D^1-X with an alcohol of formula A-D^1OH, or by reaction of an alkanol of formula HO-D^1-X with an acid of formula A-D^1-CO_2H, wherein A, and X are as previously defined and D^1 is as previously defined for D or it may be a direct bond, with the proviso that the number of atoms in the chain linking A to the phenyl ring does not exceed 5; or

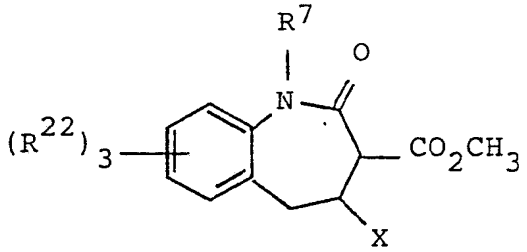
e) for compounds of the formula (I) wherein B contain a -NR^{19}CO- (amide) group and up to three further carbon atoms in the chain linking A to the phenyl group, either by reaction of an amine of formula A-D^1-NHR^{19} with an acid of formula HO_2C-D^1-X, or by

reaction of an acid of formula $A-D^1-CO_2H$ with an amine of formula $R^{19}NH-D^1-X$, wherein A, D^1 and X are as previously defined and R^{19} is H or C_1-C_4 alkyl, with the proviso that the number of atoms in the chain linking A to the phenyl ring in X does not exceed 5; or

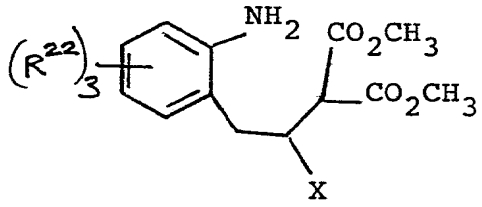
f) for compounds of formula (I) wherein A is a saturated nitrogen-containing heterocyclic group and B contains a carbonyl group together with up to four further carbon atoms in the chain linking A to the phenyl group, by reaction of the heterocyclic compound with a carboxylic acid of formula HO_2C-D^1-X, wherein D^1 and X are as previously defined; or

g) for compounds of the formula (I) wherein B contains -N= or $-NR^7-$ (amines) together with up to four carbon atoms in the chain linking A to the phenyl group and R^7 is as defined above, by reaction of an aldehyde of formula $HCO-D^1-X$ with an amine of formula $A-D^1-NH_2$ to give the schiff's base, followed by reduction to give the amine (R^7=H), followed, if desired, by alkylation or acylation to give the compounds wherein R^7 is C_1-C_4 alkyl, $CO_2(C_1-C_4)$alkyl, aryl(C_1-C_4)alkyl or heteroaryl(C_1-C_4)alkyl; wherein D^1 and X are as previously defined with the proviso that the number of carbon atoms in the chain linking A to the phenyl ring in X does not exceed 5; or

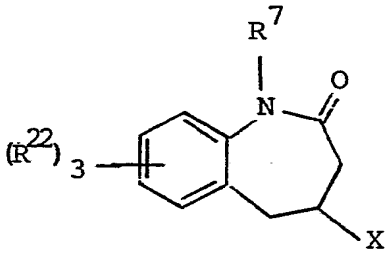
h) for compounds wherein B is a 7-membered saturated or mono unsaturated ring containing NR^7 having the formula



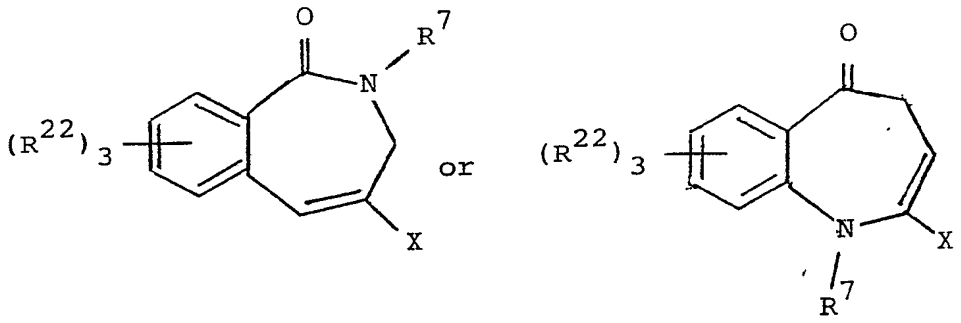
wherein R^7 and X are as previously defined and each R^{22} is independently H or an aryl group substituent as defined in A above, by cyclising a compound of the formula



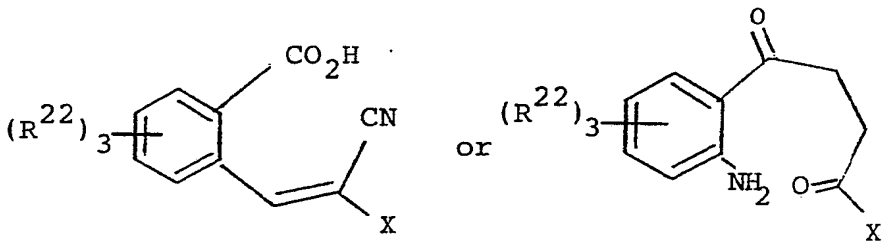
to give the product where R^7 is H, and if desired subsequently treating with lithium iodide in pyridine to give compounds having the formula



wherein R^7 is H;or for compounds having the formulae



by ring closure of the corresponding open chain compound of formulae



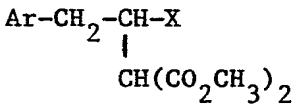
wherein R^{22} and X are as previously defined, by heating under acidic conditions to give the products wherein R^7 is H; and, if desired alkylating or acylating any of the above products where R^7 is H by reaction with a strong base followed by a C_1-C_4 alkyl halide, aryl(C_1-C_4)alkyl halide or heteroaryl(C_1-C_4)alkyl halide or (C_1-C_4 alkyl) chloroformate to give compounds wherein R^7 is C_1-C_4 alkyl, aryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)aklyl or CO_2(C_1-C_4)alkyl; or

i) for compounds of the formula (I) wherein the linking group B contains S(O)m together with up to four carbon atoms in the chain linking A to the phenyl group, and m is 0, 1 or 2; by reaction of a thiol of formula A-D^1-SH with an alcohol of formula HO-D^1-X wherein A, D^1 and X are as previously defined, in the presence of triphenylphosphine and diethylazodicarboxylate to give the thioethers where m is 0 and optionally oxidising to give the sulphone or sulphoxide derivatives where m is 1 or 2, with the proviso that the number of atoms in the chain does not exceed 5: or

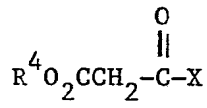
j) for compounds of the formula (I) wherein the linking group is a C_1-C_5 alkylene or C_2-C_5 alkenylene chain which may optionally be substituted by one or more OH, oxo, CO_2R^4 or perfluoroalkyl groups, either by reaction of an aldehyde of formula:

HCO-X

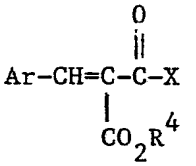
with dimethylmalonate followed by reaction with an aryl anion to give compounds of the formula:



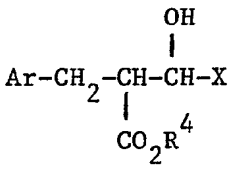
wherein Ar and X are as previously defined, or by reaction of an aryl aldehyde with a ketoester of formula:



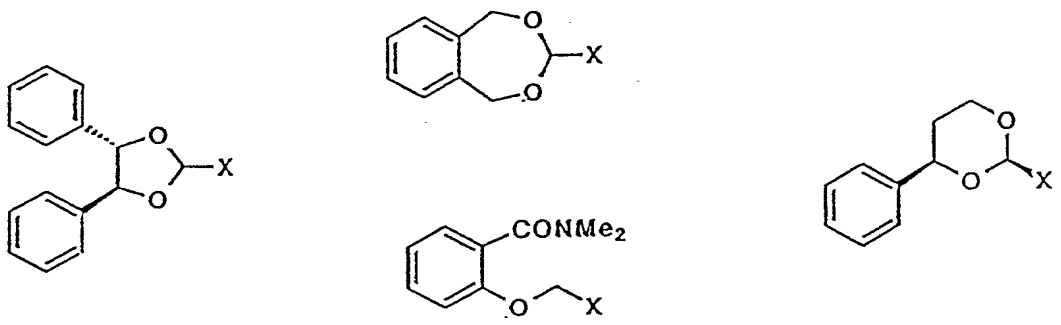
to yield compounds of the formula



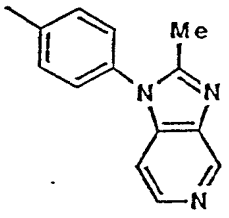
wherein R^4, Ar and X are as previously defined, followed, if desired, by reduction to give compounds of the formula:



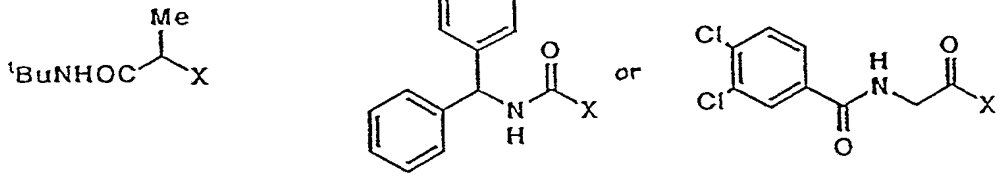
17. A process as claimed in claim 16 wherein said compound of formula I has the formula:



wherein X is:

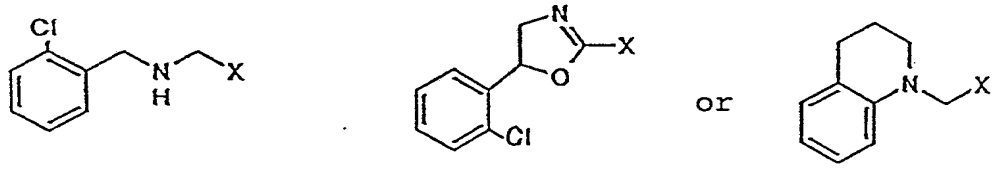


18. A process as claimed in claim 16 wherein said compound of formula I has the formula:



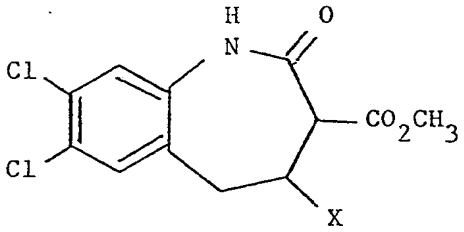
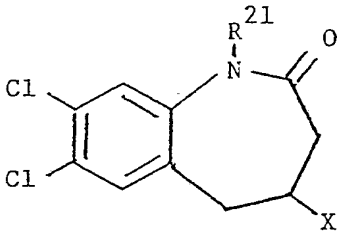
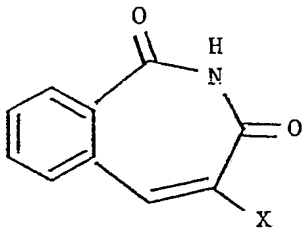
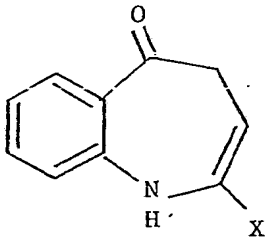
wherein X is as previously defined in claim 17.

19. A process as claimed in claim 16 wherein said compound of formula I has the formula:



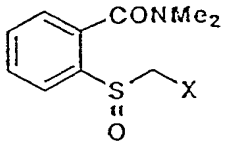
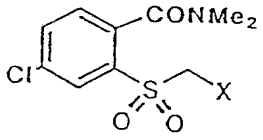
wherein X is as previously defined in claim 17.

20. A process as claimed in claim 16 wherein said compound of formula (I) has the formula:

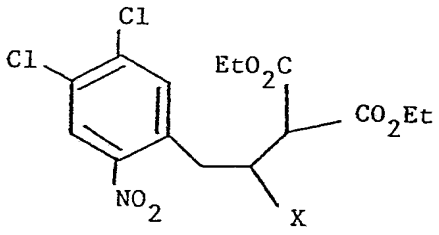
wherein R^{21} is H, methyl, 4-chlorobenzyl or 2-pyridylmethyl and X is as previously defined in claim 17.

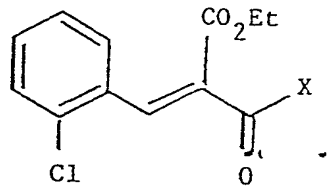
21. A process as claimed in claim 16 wherein said compound of formula (I) has the formula:


or


wherein X is as previously defined in claim 2.

22. A process as claimed in claim 16 wherein said compound of formula (I) has the formula:





wherein X is as previously defined in claim 17.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00737

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 471/04, C 07 F 7/10, A 61 K 31/435, 31/44, 31/535, 31/445, 31/47, 31/55 // (C 07 D 471/04, 235:00, 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 471/00, C 07 F 7/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0330327 (PFIZER) 30 August 1989 see claims 1,4; page 3, lines 1-41 ---	1,15
P,X	WO, A, 9010632 (PFIZER) 20 September 1990 see claims 1,5; page 1, line 1 - page 3, line 6 ---	1,15
P,X	EP, A, 0389189 (PFIZER) 26 September 1990 see claims 1,6; page 3, lines 1-35 ---	1,15
A	EP, A, 0310386 (PFIZER) 5 April 1989 see claims 1,11; page 1, lines 1-43 cited in the application	1,15

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th June 1991	27. 09. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg p.o. M. Peez

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9100737 SA 46630

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/08/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0330327	30-08-89	JP-A-	1254678	11-10-89
		US-A-	4904671	27-02-90
WO-A- 9010632	20-09-90	None		
EP-A- 0389189	26-09-90	AU-A-	5214890	01-11-90
		JP-A-	3014577	23-01-91
		US-A-	5008263	16-04-91
EP-A- 0310386	05-04-89	AU-A-	2297388	06-04-89
		AU-A-	6126190	29-11-90
		JP-A-	1113367	02-05-89
		US-A-	4935430	19-06-90